EXHIBIT C25

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO ALL CASES***	**MDL NO. 16-2738 (FLW) (LHG)**

EXPERT REPORT OF KARLA BALLMAN, Ph.D. FOR GENERAL CAUSATION *DAUBERT* HEARING

Date: February 25, 2019

Karla Ballman, Ph.D.

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1 MY QUALIFICATIONS

I am the Chief of the Division of Biostatistics and Epidemiology at Weill Cornell Medicine as well as a tenured Professor of Biostatistics in the Department of Healthcare Policy and Research. I have been working in cancer research for more than 19 years.

I received a BA degree from Macalester College in St. Paul, Minnesota with a double major in economics and mathematics. Subsequently, I received a Master's degree (S.M.) and Ph.D. in Operations Research from the Massachusetts Institute of Technology. A degree in Operations Research includes substantial training in statistics and epidemiology.

Upon receiving my degree, I was hired as a faculty member (Assistant Professor) at Macalester College to develop an undergraduate statistics curriculum and to teach statistics courses. I also was a faculty member of the Department of Statistics at the University of Auckland in New Zealand where I taught several statistics and epidemiology courses. Upon returning to the United States, I took a position at Mayo Clinic (Rochester, Minnesota) in the Division of Biostatistics and was a member of the Mayo Comprehensive Cancer Center. While at Mayo, I served as the Chair of the Division of Biostatistics and attained the rank of Professor. At Mayo, I was involved in hundreds of clinical research studies including clinical trials and observational studies. I left Mayo more than three years ago to assume the position of the Division Chief within the Department of Healthcare Policy & Research at Weill Cornell Medicine.

Over the years, I have collaborated with investigators on numerous observational studies and clinical trials. I ensure that the study design is scientifically rigorous, that the data are appropriate and of high quality, and that interpretations made are supported by the data. This work is funded primarily through peer-reviewed government grants and peer reviewed foundation grants. I am a co-investigator on numerous grants that fund cancer projects and am a co-author on more than 200 manuscripts, most of which are related to cancer research.

I have many other positions and responsibilities relevant to cancer. I serve as a Deputy Editor for the Journal of Clinical Oncology (JCO), one of the top cancer journals in the world. In this role, I obtain reviewers for submitted manuscripts that are assigned to me and evaluate whether the manuscripts are of sufficient priority for publication based on the novelty of their findings and the scientific rigor of the study design and analyses. I am responsible for the evaluation of an average of ten manuscripts per week. As a Deputy Editor, I am also consulted on manuscripts handled by Associate Editors regarding their suitability and priority for publication in JCO. Most of the manuscripts I personally handle involve assessing risk factors across a range of cancers. I also serve on numerous scientific review panels that evaluate proposals submitted for potential funding. My role on these panels is to assess proposals for their scientific rigor and their potential impact on cancer outcomes. Over the years, I have

served on more than 65 grant review panels. These include panels for government funding including the National Cancer Institute, the National Institutes of Health and Department of Defense Congressionally Directed Medical Research Programs as well as those for foundation funding such as the Damon Runyon Cancer Research Foundation and the Sarcoma Alliance for Research through Collaboration (SARC) foundation.

As mentioned, I have co-authored more than 200 peer-reviewed manuscripts, most of which address cancer-related issues. The cancer areas in which I have worked include breast cancer, prostate cancer, brain cancer, cancer in the elderly, lung cancer, sarcoma, and melanoma. The types of studies in which I have been an active collaborator include clinical trials, cancer biomarkers, and observational studies for cancer risk factors or cancer prognostic factors. My contributions include devising scientifically rigorous study designs aligned with the study objectives, performing appropriate analyses, and ensuring the interpretation of the data and subsequent conclusions are supported by the data.

Throughout my career, I have taught formal and informal courses in statistics and epidemiology for, and mentored participants in, advanced degree and postdoctoral programs.

I am being compensated at a rate of $400 per hour for my expert work in this litigation. All of the opinions in this report are stated to a reasonable degree of scientific certainty. My curriculum vitae is attached to this report, together with other required disclosures.

2 SUMMARY OF OPINIONS

2.1 STUDY DESIGNS

Epidemiological studies may be designed in a number of ways, and design affects the weight the study should be accorded in undertaking a global assessment of the available evidence. In ascending order of weight (for reasons I elaborate below), the studies I address are case reports and case studies; case-control studies; prospective cohort studies; and randomized critical trials. My focus in this report is on case-control studies and prospective cohort studies due to the very limited value of case reports and the absence of randomized critical trials concerning talcum powder exposure and ovarian cancer.

2.2 META-ANALYSIS

The term “meta-analysis” when broadly defined encompasses a range of methodological approaches for synthesizing the results of multiple individual studies. These methods include systematic reviews, pooled studies, and true meta-analyses. In this report I focus on pooled studies (which synthesize the underlying, individual patient data from published studies) and

meta-analyses (which synthesize the summary results of the individual studies and do not incorporate individual patient data) that have been performed with respect to exposure to talcum powder and ovarian cancer.

2.3 THE BRADFORD HILL FRAMEWORK

The Bradford Hill framework affords a widely accepted methodology for attempting to determine whether an association reported in the epidemiological literature reflects a causal relationship between an exposure and outcome of interest. That framework considers the epidemiological data themselves – including strength and consistency of the reported association and the existence of a dose-response relationship – as well as other considerations, including the biological plausibility of the posited relationship, the temporal relationship between exposure and disease and other factors.[1]

2.4 THE LACK OF SUPPORT FOR A CAUSAL CONCLUSION WITH RESPECT TO TALCUM POWDER EXPOSURE AND OVARIAN CANCER

In applying the Bradford Hill criteria to this context, I conclude that the evidence does not support the conclusion that cosmetic talcum powder use causes ovarian cancer. The reported association is weak, meaning that a strong demonstration of the other factors would be required to support a causal conclusion; however, no such strong showing can be demonstrated. The association reported is inconsistent, and very few studies have reportedly found a dose-response relationship. The proposed biological mechanisms by which talcum powder would cause ovarian cancer are underdeveloped and either contradicted by, or not supported by, lines of evidence that should, in the current state of cancer research, be well developed if the posited causal relationship were real. Other Bradford Hill considerations also do not support the causal hypothesis.

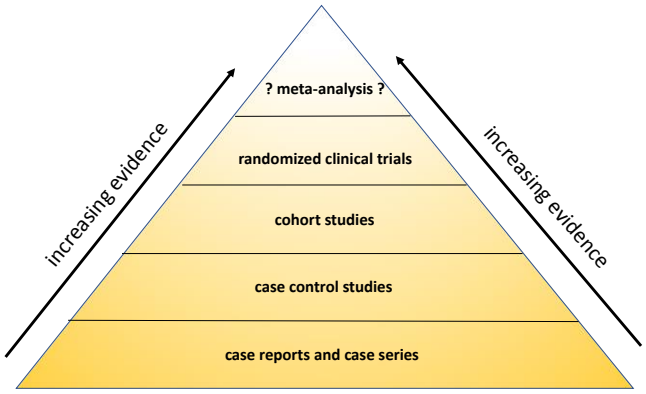
2.5 ADDITIONAL PROBLEMS WITH THE CAUSAL HYPOTHESIS

I also find that additional considerations support the conclusion that sufficient evidence for a causal relationship is lacking. I consider and reject the possibility, for example, that the epidemiological data lend further support for a causal relationship with the serous subtype of ovarian cancer. In addition, I identify several considerations that show that the best explanation for the different findings in cohort and case-control studies is that case-control studies are driven by bias and confounding. Additionally, I evaluate the evidence that has been developed since the International Agency for Research on Cancer (IARC) issued its working paper on talcum powder and show that the subsequently developed evidence only further supports the conclusion that the evidence is insufficient to support a causal relationship between talcum powder use and ovarian cancer.[2]

3 STUDY DESIGNS

There are different study designs used in epidemiology, each type with its own degree of evidence. Figure 1 illustrates the level of evidence within each trial design with increasing evidence moving up the pyramid. Each of the study designs is discussed below.

FIGURE 1: RELATIVE AMOUNT OF EVIDENCE FOR CAUSALITY BY STUDY DESIGN[1]



3.1 CASE REPORTS AND CASE SERIES

The least amount of evidence provided for a cause-and-effect relationship is provided by a case report. A case report describes a single case or two and is considered to be anecdotal in nature. In medicine, a case report provides details for an individual patient such as treatment and subsequent outcome or past exposure to an agent and the subsequent development of disease. Case reports usually describe an unusual or novel occurrence and are shared for educational purposes. By their nature, they focus on rare, unusual occurrences and are used to generate hypotheses rather than provide definitive proof of a causal relationship. Case reports by their nature are not reflective of statistical sampling from the general population. As a consequence, they are placed at the bottom of the clinical evidence hierarchy. The major value of case reports is in uncovering new diseases or rare adverse effects of treatments.

A case series identifies subjects with a known exposure and reports on subsequent outcomes. Case series may be comprised of a consecutive series of patients or a selected subsample. The sample size is generally small and only includes individuals who were exposed or treated; there

[1] The question marks around meta-analysis in Figure 1 reflect the fact that there is some disagreement as to whether meta-analyses are the highest level of evidence. It should be noted that in this figure, the meta-analysis refers to the pooling of randomized clinical trials results. A meta-analysis of observational data falls below that of individual clinical trials.

is no control group. An example of a case series would be a group of 20 women with ovarian cancer who had used talcum powder on their perineum prior to developing ovarian cancer. By their nature, case series are descriptive. They also generate hypotheses rather than testing hypotheses, and are not used to establish cause and effect. A major disadvantage of a case series is that this design generally suffers from selection bias. This means that the patients in the case series usually do not appropriately represent the wider population of patients For example, a case series that reports on women with ovarian cancer who used talcum powder perineally likely does not represent the population of all women exposed to talcum powder and likely does not represent all women who developed ovarian cancer. Another issue with case series is that they lack a comparator group. Specifically, if the rates of perineal talcum powder use are similar between women who develop cancer (cases, who are in the series) and women who do not develop ovarian cancer (controls, who are not part of the series), there would be no evidence of an association or causal effect. However, since there are no controls in case series, it is not possible to make this comparison or identify an association between exposure and disease. Case reports and case series studies are not included in this report.

3.2 CASE-CONTROL STUDIES

A case-control study is an observational study that identifies two group of individuals: those with the outcome of interest (cases) and those without the outcome of interest (controls). The groups are compared to determine whether they differ with respect to an exposure of interest. These studies provide a higher level of evidence than case reports or case series because of the inclusion of a comparator group, the controls. An example of a case-control study is one where the cases are women with ovarian cancer and controls are women without ovarian cancer with the exposure of interest being perineal talcum powder use.

Well-conducted case-control studies use a pre-specified protocol that indicates how the cases and controls are to be identified and specifies how to measure the exposure. In theory, it should be possible for other investigators to use the protocol and obtain the same cases (with similar controls) and reproduce the values for the exposure of interest. Controls are often matched to cases on important aspects relevant to the outcome of interest. For example, since older women are more likely to develop ovarian cancer than younger women, a well-designed case-control study will select a control who is the same age as the case at the time she was diagnosed with ovarian cancer. The purpose of matching is to ensure that groups of cases and controls only differ with respect to the exposure of interest. For the question of perineal talcum powder use and ovarian cancer, the ideal case-control study would be one that matched controls to the cases with respect to all characteristics known to be associated with the risk of ovarian cancer, other than the exposure of interest (in this instance, perineal talcum powder use). If the groups of cases and controls appear similar on factors known to be associated with

ovarian cancer risk other than perineal talcum powder use, the association of perineal talcum powder use with ovarian cancer risk can be better isolated (unknown factors always remain a concern).

The advantage of a case-control study is that it can be accomplished in a relatively short period of time. Because the outcome status of the participants is already known at the start of the study, the participants do not need to be followed for a length of time to obtain a sufficient number of individuals with the outcome. All that needs to be collected or measured is the exposure of interest and potentially other variables relevant to the outcome of interest. A case-control design is a particularly attractive design for the study of outcomes that are relatively rare since it ensures that there will be a sufficient number of participants with the outcome, yielding adequate power. Power is the likelihood of detecting an association when there is an association to be detected. If a study has 80% power to detect a risk ratio of 1.3, this means that if the risk ratio is 1.3 or higher in reality, there is an 80% chance that the association will be statistically significant (i.e., it has a p-value ≤ 0.05). This is in contrast to a prospective cohort study (discussed next), which generally requires the recruitment of a large number of participants to ensure a sufficient number will develop the (relatively rare) outcome of interest. Both types of studies can be designed to have adequate power.

The major disadvantage of a case-control study is that it generally is not possible to ensure that the group of cases is similar to the group of controls on all aspects related to the outcome other than the exposure of interest. Most often, it is only possible to match cases to controls on two or three characteristics. Otherwise it becomes extremely difficult to find controls or becomes quite expensive in terms of having to obtain additional measurements of these variables on the participants. Many of the case-control studies that evaluate the association between perineal talcum powder use and ovarian cancer risk typically only match on a small subset of risk factors of ovarian cancer, e.g., age and location of residence. Examples of this include the Ness 2000[3] study (which frequency matched cases to controls by five-year age groups and three digit phone exchanges as a surrogate for residence), the Schildkraut 2016[4] study (which frequency matched controls to cases on residence and age), and the Cramer 2016[5] study (which frequency matched controls to cases by five-year age groups and region of residence). The inability to match the case group to the control group on all risk factors for ovarian cancer results in residual confounding. For example, suppose a case-control study matched cases to controls on the basis of age and location of their residence. The controls are likely to differ from the cases with respect to other important risk factors for ovarian cancer such as nulliparous status or BMI. If it is the case that obese women are more likely to apply talcum powder in the perineal region and that there is a greater proportion of obese women among the cases, then it cannot be ascertained whether any increased risk of ovarian cancer is attributable to obesity, perineal talcum powder use or both (or is unrelated). Obesity status and perineal talcum powder use

would thus be confounded in this example. There are statistical methods that can reduce the level of confounding, but they cannot eliminate it.

Case-control studies also suffer from biases inherent in the study design. One bias briefly mentioned above is *selection bias*. This occurs when cases and controls are selected in such a manner that they differ on important risk factors associated with the outcome other than the exposure of interest. To avoid such selection bias, the cases and controls would need to be similar with respect to all known risk factors associated with the outcome. This is difficult, if not impossible, to achieve in a case-control study. Sometimes it is just not possible to measure all the known risk factors, and even if it were, not all risk factors for ovarian cancer are known. Another common bias in case-control studies is *recall bias*. Recall bias occurs when cases and controls remember past exposures in a differential manner; e.g., cases might be more likely to remember an exposure than a control. If a woman knows she agreed to be in a study evaluating the association between ovarian cancer and perineal talcum powder use, for example, there is a likelihood that a case will recall perineal talcum powder use in greater proportions than controls, even if the usage rates between the groups is the same. Specifically, it has been documented that cases remember exposures to putative risk factors differently from controls[6] because of the desire to explain why they in particular got the disease. In studies of risk factors for breast cancer, women who have had the disease recalled a greater variety of risk factors they had been exposed to, including those falsely attributed to the disease in the media, such as use of oral contraceptives[7] and previous abortions.[8] This is a particular concern in the talcum powder literature because many of the case-control studies did not blind the women as to the purpose of the study, creating a risk of recall bias, in that the cases are more likely to recall potential putative risk factors, such as perineal talcum powder use, with a greater likelihood than controls. Recall bias of this type would generate an exaggerated association between perineal talcum powder use and ovarian cancer. If women with a disease become aware of a potential association between a risk factor and their disease, it would also increase the amount of recall bias. This is an even bigger concern for case-control studies conducted after lawyers began running advertisements regarding the prospect of litigation for women with ovarian cancer who used talcum powder products and after the publicity surrounding outcomes of court cases involving ovarian cancer and talcum powder use.[4] It should be noted that there is no statistical technique that can reduce or eliminate the effects of this bias.[9]

3.3 PROSPECTIVE COHORT STUDIES

Generally, in my experience, prospective cohort studies yield a higher level of evidence than case-control studies. A prospective cohort consists of a group of participants who differ with respect to certain factors under study and who are followed longitudinally over time. The goal is to determine how the factors of interest are associated with a certain outcome. A prospective

cohort study minimizes differential selection bias because cases and controls are selected prior to knowing the outcome of interest. Such studies also minimize recall bias because the exposure of interest is measured prior to the outcome, which limits the likelihood of differential recall between cases and controls.

A disadvantage of a cohort study is that the cohort needs to be quite large for outcomes that are relatively rare. The number of participants required for a cohort study is usually orders of magnitude larger than that for a case-control study. This substantially increases the resources needed to conduct the study since the exposures of interest and outcomes need to be measured on all the participants. Prospective cohort studies also require a longer time to conduct because the participants are followed longitudinally for outcomes that have not yet happened. Some outcomes of interest may require years to develop. Another potential disadvantage is that cohort studies are used to address multiple research questions, and this means that the exposure of interest may not be measured in the same way as it would if it were the only primary research question. However, this concern depends on the specific research questions of interest, and in general, it is an advantage to be able to measure exposure before the outcome is known.

There are several cohort studies evaluating the association of perineal talcum powder use and ovarian cancer.[10-13] All the cohort studies are large, with some having a sufficient number of women who were diagnosed with ovarian cancer to yield adequate power. Indirectly, this means that they have sufficient follow-up. First, many of the cohort studies recruited women who were 30 years or older: the Nurses' Health study recruited women in 1976 who were between the ages of 30-55 years, the Women's Health Initiative recruited women between 1993 and 1998 who were between the ages of 50 to 79 years, and the Sister Study recruited women between the ages of 35 to 74 years in 2003-2009. Because ovarian cancer is a disease of older women with a median age at diagnosis of 63 years, it would not require decades of follow-up to observe a sufficient number of cases. Second, it is reported that most women who use talcum powder started doing so when they were in their early adulthood.[5] Hence, there would be a sufficient time from time of exposure to allow for the development of ovarian cancer, if talcum powder use was a causal agent. One drawback of the cohort studies is that perineal talcum powder use was measured only at a single point in time, which raises the concern that women would be misclassified with respect to perineal talcum powder use if they started using it after they were asked about talcum powder use at the initiation of the cohort study. But the fraction of women who were misclassified because of this is likely quite low given that the mean duration of perineal talcum powder use in women that are ever-users is greater than 20 years, as reported in some case-control studies.[14] In addition, if women started after they were asked about use in the cohort study, the limited amount of follow-up time in the cohort studies would minimize the impact of misclassification under plaintiffs' experts' own

theories because they have taken the position that the lag time between exposure to talc and the alleged development of ovarian cancer from it is on the order of decades.[15] Finally, most of the prospective cohort studies did collect information on duration or frequency of use, which allows for an evaluation of dose-response.

Notably, most studies (both case-control and cohort) evaluated the perineal talcum powder exposure as ever versus never, even when they also investigated a dose-response relationship. This means it is possible to compare the observed association between ever versus never perineal talcum powder use between case-control studies and cohort studies. If there is a dose-response relationship, it should not depend on how the amount of exposure to perineal talcum powder is measured. It would be expected that if there is a dose-response relationship, it would be reflected as a higher likelihood of developing ovarian cancer cases with greater frequency of use, longer duration of use, or a larger cumulative number of doses. There is no evidence that the instruments used in the case-control studies to assess perineal/genital talcum powder exposure are more accurate than those used in the cohort studies.

3.4 Randomized Clinical Trials

Randomized clinical trials are considered a gold standard of evidence for a causal relationship because trial participants are randomly assigned to receive the treatment being evaluated or to receive the standard treatment (or placebo treatment if ethical). Randomization ensures that individuals who eventually develop the disease and those who do not are selected in the same way (i.e., it minimizes selection biases), similar to prospective cohort studies. However, the most important aspect is that it minimizes the chance that there are meaningful differences between the two groups with respect to risk factors for the outcome. It is the best method available to ensure that the two groups are similar on all risk factors other than the assigned treatment. This allows the researchers to isolate the treatment effect for the treated group when compared with the no treatment group because other variables are kept constant.

Generally, it is not feasible to perform a clinical trial to ascertain whether something is potentially harmful. Trials are conducted to evaluate the benefit of an intervention. Often times, potentially harmful effects of an intervention are observed in trials designed to evaluate the benefits of the intervention. These are recorded as adverse events, which essentially are unintended, detrimental effects. There have been no trials performed to determine the benefits of perineal talcum powder use. Hence, there are no randomized data that are relevant to assess potential adverse effects of perineal talcum powder use, such as the development of ovarian cancer.

Finally, meta-analyses of randomized clinical trials are sometimes considered to be the highest level of evidence, but this is not universally accepted.[16-19] Regardless, only meta-analyses of

randomized trials are purported to be the highest level of evidence and not meta-analyses of observational data (i.e., case-control studies or prospective cohort studies). The next section covers meta-analyses in more detail.

4 META-ANALYSIS

The term meta-analysis may encompass several distinct study designs. Designs relevant to this report are systematic reviews, pooled studies and meta-analyses.

4.1 SYSTEMATIC REVIEWS

A systematic review is a comprehensive, reproducible search for primary studies on a focused clinical question. High-quality systematic reviews are conducted according to a pre-specified protocol. The first step is to delineate a process for conducting a comprehensive search for relevant studies. Such a search yields a list of all studies that may potentially be relevant and generally is quite a large list. After all studies have been identified, they are reviewed and selected for inclusion in the systematic review according to transparent eligibility criteria that are contained in the protocol. Often times, the list of included studies is considerably smaller than the initial list because when reviewed for content, many studies are not relevant to the research question of interest or do not meet the pre-specified eligibility criteria. The purpose of a protocol is to ensure that a different set of researchers can use the protocol and arrive at the same set of studies.

Once all the studies have been identified, they are often assessed for quality, again using transparent and explicit criteria. Each study is then assigned a quality assessment, often a numerical value. The final step is to synthesize the information across the studies. This can be done in a qualitative fashion by summarizing in a narrative the information and quality of information contained in the studies and drawing conclusions based on this information. However, the information is often synthesized quantitatively to yield a single estimate of an effect size or the strength of an association, such as between perineal talcum powder use and ovarian cancer risk. The mathematical process that combines the results is essentially a weighted average of the results in the individual studies using the quality score, study sample size, or some combination as the weights. The process of quantitatively combining the results is called a meta-analysis.

4.2 POOLED STUDIES

Individual participant data studies, often called pooled studies, are those that use participant level data from published, and sometimes unpublished, studies. This is in contrast to meta-analyses that only combine the summary values that are available within the published

manuscript; a meta-analysis does not have access to the patient values that yielded the summary values. An advantage of a pooled study is that it can better adjust results for confounding variables than can be done in a meta-analysis. For example, suppose there are two studies, one of which reports an association (say an odds ratio) adjusted for the age and nulliparous status of the woman, and the other of which reports an adjusted odds ratio for age and place of residence of the woman. A meta-analysis would average these two adjusted risk ratios even though they are adjusting for different sets of variables. On the other hand, a pooled study would have access to the individual participant data of these two studies and – if both studies collected information on age, nulliparous status, and residence for each woman – would allow the researcher to compute an adjusted risk ratio that appropriately adjusts for all three factors.

Another advantage of a pooled study over a meta-analysis is that it is often possible to perform different subgroup analyses that are not feasible in a meta-analysis. For example, a meta-analysis might provide results of perineal talcum powder use according to different applications such as dusting of sanitary napkins, dusting of underwear, or direct application to the perineum, but it might be that not every individual study provides results for the different types of applications. If the individual patient level data were available to the researcher and both studies did record the type of perineal application, the researcher could compute the associations for each type of application across the pooled studies. In the studies considered in this report, there was a single pooled study, by Terry et al.[20]

4.3 META-ANALYSIS

The purpose and some of the capabilities and limitations of meta-analyses have already been alluded to in the preceding sections. In summary, a meta-analysis attempts to evaluate the effect of an exposure by combining the effects reported in published studies. Unlike pooled studies, meta-analyses are not premised on individual patient data, and instead rely on the summary values reported in the publications. Nevertheless, meta-analyses of the same underlying studies can produce widely varying results depending on a range of factors, including, in particular, the studies that are included and how to weigh them.

In theory, a well-designed meta-analysis that draws from a robust pool of individual studies should provide high-quality evidence concerning an association. Indeed, as mentioned above, some have proposed that meta-analyses of randomized clinical trial data are the highest level of evidence. But there is disagreement on that point and research that illustrates some of the limitations of meta-analyses. For example, there have been several studies conducted that compared the results of a meta-analysis of several small randomized trials and a subsequent large randomized trial.[21] Those studies found that the meta-analysis results would have led to the adoption of an ineffective treatment in 32% of the cases or led to the rejection of a useful

treatment in 33% of the cases. Publication bias would lead to a false positive result, meaning the meta-analysis indicated the treatment was effective (i.e., statistically significant difference) and the subsequent randomized trial did not detect a difference in effectiveness between the treatments. Publication bias arises from the tendency for investigators to preferentially submit studies with statistically significant results, and for editors to accept them. Although it is possible to test for publication bias, these tests are often underpowered.

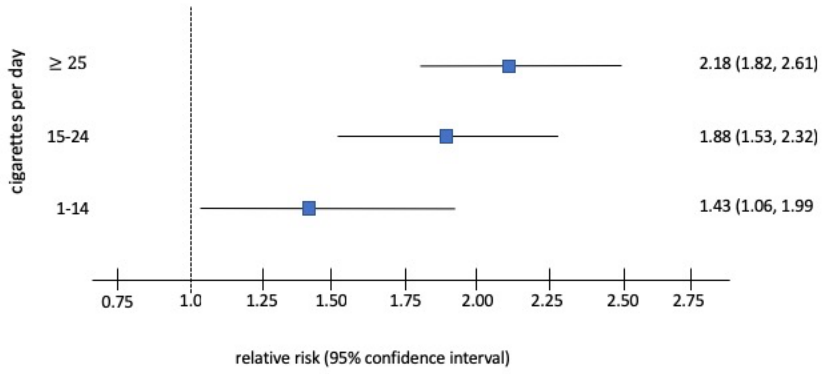
Another potential problem with meta-analyses is that the results of meta-analyses are considerably influenced by subjective choices made by the authors.[22] Specifically, when investigators perform a meta-analysis, they make decisions regarding (1) the primary studies that are included, (2) the effect measures that will be used (e.g., relative risk of the outcome, difference in the proportion of patients with the outcome, etc.), (3) the choice of the quality assessment scale, and (4) the choice of the averaging technique that will be used to combine the summary values across the studies. Different investigators may make different choices, which would lead to different estimates. Of considerable concern is determining whether studies are similar enough to be included in a meta-analysis. Often investigators choose to only include a very narrow range of studies, such as only clinical trials or only case-control studies, because other types of studies yield differing results. This is problematic because it is instructive to understand what the differences imply, which may often be the consequence of biases inherent in different types of study design. Specifically, it may be the case that the analysis is not meaningful if there is discordance between the results of different study types, such as case-control studies and cohort studies. This has led researchers to advocate more reliance on the Hill criteria (discussed further below) and less deference to meta-analysis. As one article explained, "meta-analyses ought not be considered the best kind of evidence for assessing causal hypotheses in medicine" because they rely on a narrow range of evidentiary diversity.[22] By contrast, Hill's framework should be employed, since it considers all evidence available (case-control studies, cohort studies, randomized trials, animal studies, cell line studies, etc.).

Finally, meta-analyses are particularly suspect when they combine observational data, as opposed to randomized trial data. This is so because "[d]ue to the effects of confounding and bias, such observational studies may produce estimates that deviate from the true causal effects beyond what can be attributed to chance."[23] "Combining a set of epidemiological studies will thus often produce spuriously precise, but biased, estimates of association."[23] Confounding and differential measurement error are serious problems in studies of exposures that are linked to lifestyle. When Ioannidis et al.[24] compared the results of randomized versus non-randomized studies, they found that discrepancies beyond chance were observed. Specifically, the differences observed between the randomized studies and non-randomized studies were found to be statistically significant in 16% of the studies. The study also found that differences in estimated magnitude of associations are common, with 33% of the studies having

a two-fold difference between the randomized trials estimate and non-randomized studies estimate of the odds ratio, and 62% having a 50% difference in the odds ratio.

The concerns about biases in observational studies and meta-analyses of observational studies are not just theoretical. A meta-analysis of four prospective studies of middle-aged men explored smoking as a risk factor of suicide.[16] All the cohort studies showed a positive association between smoking and suicide. A meta-analysis of the cohort studies based on approximately 390,000 men demonstrated a dose-response relationship, with increasing number of cigarettes smoked per day associated with increased risk of suicide (Figure 2). It would be tempting to conclude that the association is causal due to the demonstrated dose-response relationship in the meta-analysis and consistency of the risk ratios of the association across the cohort studies, if there would have been a plausible explanation (but there is none).[25] Instead, the observed association is likely due to confounding of risk factors for suicide and smoking status, such as the fact that individuals with increased anxiety are more likely to commit suicide and are more likely to smoke.

FIGURE 2: ASSOCIATION BETWEEN NUMBER OF CIGARETTES AND SUICIDE



One of the most important biases that exists in case-control studies relative to cohort studies is *recall bias*. For example, a comprehensive meta-analysis showed an association between higher intake of saturated fat and risk of breast cancer.[26] However, while a meta-analysis of the 12 ***case-control*** studies showed a statistically significant association between increased intake of saturated fat and increased breast cancer risk (risk ratio of 1.36), there was no association observed in a meta-analysis of six ***cohort*** studies (non-significant risk ratio of 0.95). The discrepancy between the case-control studies and cohort studies is likely due to recall bias from the dietary items and selection of the study participants, yielding a spurious association in the case-control studies.[27] Simply put: women with breast cancer are more likely to remember engaging in potentially unhealthy activities like eating saturated fat.

Since all the meta-analyses for evaluating the purported association between use of perineal talcum powder and ovarian cancer are based on observational studies, the large majority of which are case-control studies, caution must be employed in drawing conclusions from those meta-analyses since "…even if adjustments for confounding factors have been made in the analysis, residual confounding remains a potentially serious problem in observational research."[16] In addition, when there are differences in the magnitude of an association between case-control studies and cohort studies, it does not make sense to combine them in a single summary. As discussed above, case-control studies have more biases than cohort studies. If there are a greater number of individuals in case-control studies than cohort studies, the result of combining all studies will naturally reflect the associations seen in the case-control studies due to their larger sample sizes. Hence, this will mask the difference in results between the lower level of evidence case-control studies and the higher level of evidence cohort studies. When there are differences in terms of magnitude of associations and statistical significance of associations between case-control studies and cohort studies, the meta-analysis should be stratified by the study type, with a case-control study meta-analysis summary and a cohort meta-analysis summary. As stated by Feinstein,[19] "[w]ith meta-analytic aggregates, however, the important inconsistencies are ignored and buried in the statistical agglomeration." This is especially true if there are considerably more studies of one type, as is the case here.

Although implausibility of results can sometimes protect against reaching misleading claims, it is surprisingly easy to produce reasonable explanations for causality even when causality is absent. In studies of the association of beta carotene and risk reduction of cardiovascular disease and cancer, a plausible hypothesis is that beta carotene has antioxidant properties and therefore prevents carcinogenesis and atherogenesis by reducing oxidative damage to DNA and lipoproteins.[28] This hypothesis was consistent with the results of a meta-analysis of observational studies that found a statistically significant reduction in cardiovascular deaths between individuals in the high beta carotene group compared to those in the low beta carotene group. However, a meta-analysis of clinical trials randomizing participants to beta carotene supplements versus no supplements found a statistically significant 12% increase for cardiovascular death. Similar discrepancies between the analysis of the observational studies and randomized trial data were observed for the cancer outcome.[16] The subsequent conclusion was that there is no evidence of beneficial effects of beta carotene supplements in terms of reduction in cardiovascular disease and cancer incidence.

5 APPROACH

The main focus of this report is whether perineal exposure to talcum powder causes ovarian cancer. As mentioned previously, the gold standard for answering that question would be a randomized trial that would randomly assign women to a group that would apply talcum

powder to the perineum after bathing or to a group that would apply some other powder (say cornstarch) to the perineum after bathing. Ideally, the women and investigators would not know the group to which a participant was assigned. The women would then be followed over a long period of time and assessed for ovarian cancer. Such a trial would not be feasible, however, for several reasons. The first is that if it is felt by some that perineal talcum powder use causes ovarian cancer, it would not be ethical for them to enroll in the trial. Even beyond that, given the fact that ovarian cancer incidence is so low, it would not be feasible to conduct this trial in terms of the number of patients (thousands) that would need to be recruited and the length of follow-up that would be needed. The trial would need to enroll women with no exposure to perineal talcum powder and then randomize them between continue not to use or to start use. It could potentially be difficult to find women with no exposure if the true exposure rate is as high as 50%, as reported by some studies and knowing that less than 3-5% of eligible people choose to participate in a clinical trial. The length of treatment would likely need to be quite long, which means there would be issues of non-compliance. Finally, by the time the trial were completed with the requisite number of observed ovarian cancer cases, it would be decades later and the question would probably no longer be of interest. In addition, there are no randomized data regarding the development of ovarian cancer as an adverse event associated with perineal talcum powder use. To date and for the foreseeable future, the only available human data with respect to the evaluation of an association between perineal talcum powder use and ovarian cancer are from observational data: case-control studies and cohort studies.

As between these two types of observational data, the level of evidence for establishing causality is greater for prospective cohort studies (see Figure 1). As indicated, prospective cohort studies minimize biases such as recall bias and participant selection bias, which is why they have a higher level of evidence than case-control studies. Based on my experience, there needs to be overwhelming and compelling evidence to overcome the scientific consensus and conclude that case-control studies offer a higher level of evidence. Absent such compelling circumstances, if there is a conflict in results between prospective cohort studies and case-control studies, it is scientifically justified to place more weight on the results from the prospective cohort studies, since they have fewer biases than case-control studies.[29]

5.1 Bradford Hill Framework

The framework I use for evaluating the evidence of whether perineal talcum powder exposure causes ovarian cancer is that proposed by Bradford Hill.[1] The framework is meant to be applied to all available, relevant data, including cell line data and animal data, as well as human data. The more aspects of the framework that are met, the greater the likelihood of a causal relationship. There is a greater certainty of a causal relationship between an exposure and

outcome when more of the evaluated criteria are met. In addition, the strength of the observed association between exposure and the outcome influences how demanding the remaining criteria in the framework are in evaluating whether a causal relationship exists. Specifically, if the human data consists primarily of observational data and the observed association is small to modest (say a risk ratio less than 2.0), there needs to be more compelling evidence on the other Bradford Hill factors to support a causal relationship because it is known that residual confounding is more likely to yield small to modest associations than is causality. Hence, observational studies that yield small to modest levels of association require a higher level of supporting evidence to reach a conclusion of causality than do studies with strong levels of association.[30,31]

5.1.1 STRENGTH OF ASSOCIATION

This criterion evaluates the strength of the relationship between the exposure and the outcome. Hill explained that "the larger an association between exposure and disease, the more likely it is to be causal."[32] A classic example is the investigation of scrotal cancer incidence in chimney sweeps. The rate of scrotal cancer was nearly 200 times greater in chimney sweeps than in other occupations.[32] This ultimately led to a determination that chimney soot likely causes scrotal cancer. On the other hand, Hill suggested that small associations are less likely to be causal because they could more conceivably arise from other factors, such as bias and confounding. In fact, there have been such examples, like the observed, statistically significant, associations between smoking (the exposure) and suicide (the outcome) cited earlier that was not found to be causal.

Today, researchers have the ability to collect much larger datasets and have access to a greater number of publications, which leads to quite small associations being statistically significant. As such, statistically significant results are not always biologically meaningful or methodologically appropriate for inferring causality. If the small association arises from observational data, rather than randomized data, further evidence is required to demonstrate that this is not merely a spurious result arising from confounding or biases. This is not to say that small associations are never indicative of a causal relationship, but rather that they require a thorough examination of the underlying study design, "comparison to the weight of evidence in the literature, and consideration of other contextual factors, including the other criteria" listed below.[32]

In terms of applying this criterion, it is meant to be the association between exposure of interest and the outcomes. Specifically, a relative risk of 1.2 to 1.3, which is what is reported in most of the meta-analyses I reviewed, is a relatively weak association. This is true regardless of how serious or prevalent the outcome of interest may be. Contrary to the suggestions of several of plaintiffs' experts, the ultimate impact that a relative risk may have on public health

is not relevant for the ascertainment of this criterion. Specifically, to determine the impact on public health, one needs to assume that the association is causative. If it is not causative and only the consequence of confounding, removing the exposure would not reduce the outcome because it is not causative. For this reason, it is circular reasoning to measure the strength of the association in terms of its potential to be causal based on the impact on public health.

5.1.2 Consistency

This factor requires that multiple studies across different locations, populations, and study designs show a similar association between the exposure and the outcome.[1] Results across studies are consistent if the risk ratios are numerically close to one another and the results are statistically significant in most studies. Note that it is not necessary that all studies have statistically significant results since the p-value, which is a measure of the likelihood that results occurred due to chance, is considerably influenced by the sample size. Smaller studies have less power, meaning that even if a smaller study has the same risk ratio as a larger study, the p-value of the smaller study may be larger than 0.05, or non-significant. However, if adequately powered studies do not achieve statistical significance, this is evidence of inconsistency. Another way inconsistency can arise is if the 95% confidence intervals for the risk ratio estimates have no to little overlap with one another. For adequately powered studies, if one study has a statistically significant result and the other does not, it means that the magnitude of the relative risk differs considerably, which is an inconsistency between the size of the estimated relative risks.

When evaluating observational data, it is also important to have similar results across the different study designs; that is, the results for case-control studies and cohort studies should be numerically similar and statistically significant if adequately powered. In the situation where the case-control studies are generally consistent but differ from results of the cohort studies, which are generally similar to each other, this criterion is not met. If an association is truly causal, it would be observed regardless of the type of study design. When the results across study designs are not consistent, i.e., case-control studies report a statistically significant association and cohort studies do not, the study with the accepted higher level of evidence is the cohort study because it eliminates biases such as recall bias.

5.1.3 Specificity

When this was proposed, it meant that associations are more likely to be causal when the exposure causes only one disease. This criterion was proposed in an era when exposure was often defined in terms of proxies for the true (often unknown) factor. Examples are occupation (e.g., chimney sweep) or residential location. Today, exposures are defined at a much finer level, such as the dose of a specific chemical. Oftentimes, the exposure being evaluated can be associated with numerous diseases or a disease arises as a result of a number of different

exposures, or even a mix of exposures. While there are examples of highly specific exposure-disease associations, the original criterion of specificity is widely considered weak or irrelevant in modern epidemiology.[32]

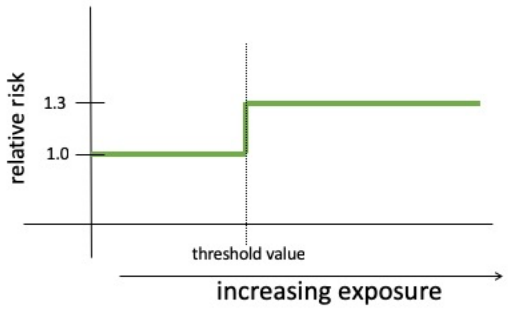
5.1.4 Temporality

For an association of an exposure to a disease to be causal, the exposure must precede the onset of the disease. There is universal agreement among epidemiologists that this criterion must be met for an exposure to cause a disease. Sometimes it is difficult to ascertain whether this criterion has been met if the disease and exposure are measured in close proximity of one another. For example, suppose it is suspected that a drug causes a cancer and that an individual was prescribed the drug six months before their cancer was diagnosed. In this example, it is unlikely that the drug caused the cancer, although the individual did start taking it prior to being diagnosed, because cancer tends to have long latency periods. Due to the healthcare interaction, the individual likely may have undergone additional examinations at the time they were prescribed the drug or during follow-up for the treatment that led to discovery of the pre-existing cancer. Therefore, even though exposure preceded the diagnosis, it is unlikely that the drug exposure caused the disease; instead, it is likely that the exposure only preceded the diagnosis of cancer, not the cancer itself. This can be labeled as temporal ambiguity or detection bias.

5.1.5 Biological gradient

A biological gradient – or dose response – is present where the risk observed depends on the degree of exposure. Hill stated that "if a dose response is seen, it is more likely that the association is causal." In particular, the demonstration of a dose-response relationship provides clear evidence of a causal relationship. The most commonly assumed relationship is monotonic, which means that increasing doses are associated with increasing risks. However, there are more complex dose-response relationships, such as a threshold model. In that model, the disease risk only increases once the exposure hits a specific level and then remains constant for further increases in dose (Figure 3).

FIGURE 3: EXAMPLE OF A THRESHOLD DOSE-RESPONSE RELATIONSHIP



Regardless of the nature of the dose-response relationship, it needs to be demonstrated consistently across the available studies. Specifically, the same type of dose-response relationship needs to be exhibited in the different studies. If a threshold relationship is hypothesized, it would require evidence of the threshold value as well, and the value is similar across the studies. If only a few studies exhibit a dose-response rather than all, this criterion would not be convincingly met.

5.1.6 PLAUSIBILITY

This criterion is satisfied if the observed association is consistent with the available information and knowledge regarding the etiology and mechanism of disease. The state of knowledge of disease mechanisms and the tools available to researchers today are considerably more sophisticated and advanced compared to the era in which Hill proposed this criterion. They allow researchers to posit and test more aspects of the exposure-to-disease pathway. As such, this criterion plays a greater role in establishing causality than in previous decades and will continue to grow in importance as scientific advances continue to be made. Specifically, researchers are better able to predict plausible relationships using in vitro and in vivo models that isolate defined disease mechanisms, which represents a paradigm shift in how evidence for causality is obtained.[32] Plausibility requires support from biological or mechanistic studies. It cannot just be something that sounds reasonable. Without supportive biological data, the criterion is not satisfied.

5.1.7 COHERENCE

Hill proposed that there should be coherence between epidemiology and laboratory findings. An example of this would be that if a dose-response relationship is proposed, based on the epidemiology studies, it is not contradicted by evidence arising from cell line and/or animal studies.

This criterion is closely related to biological plausibility in that the evidence of a causal effect of an exposure should make logical sense based on all the available information, consistent with biological plausibility evidence. Specifically, evidence for a causal association requires coherence across all the available data; e.g., cell line, animal and human data. If there are contradictions among the available information, it cannot be concluded with reasonable scientific certainty that the association between the exposure and disease is causal.

5.1.8 Experiment

Hill stated: "Occasionally it is possible to appeal to experimental evidence." In this context, he primarily meant randomized trials in humans. As discussed, there are no randomized data available regarding perineal talcum powder exposure and ovarian cancer, and likely such data will not become available in the future. Hill also explained that in addition to randomized trials that assign individuals to the exposure or not, another set of evidence would be that disease risk declines following the cessation of an exposure. Although such an experiment might be feasible for perineal talcum powder use and ovarian cancer, it may not result in observable decreases in ovarian cancer incidence. It is likely that ovarian cancer follows a complex development pathway and cessation of perineal talcum powder exposure (even if such exposure is posited to be a cause of cancer) may not reverse or appreciably slow the progression toward the development of ovarian cancer.

5.1.9 Analogy

This criterion essentially means that when there is strong evidence of a causal association between a particular exposure and a specific disease, investigators should be willing to accept weaker evidence when evaluating whether a similar exposure causes a similar disease. One example where this criterion was successfully satisfied is with respect to the health risks of second-hand cigarette smoking. There is considerable similarity between primary and secondary cigarette smoke exposure and the subsequent disease that develops after exposure is the same. Hence, the level of evidence for causality was lower for second-hand smoke than for establishing a causal relationship between primary cigarette smoking and various diseases, including a smaller strength of the association.

While lack of analogy does not preclude causation, invoking it does not necessarily support causation, especially because a substantial body of knowledge exists to identify an analogy for almost every situation.

5.2 Approach for Forming My Opinion

My opinion is based on a review of all the relevant epidemiology literature relevant to evaluating the association between perineal talcum powder use and ovarian cancer. I considered case-control studies, prospective cohort studies, and meta-analyses; I did not find

any data arising from randomized trials of talcum powder. I did not read or evaluate case reports or case series given the low strength of evidence provided by such studies. Since all the epidemiology studies are observational, I carefully considered the amount of evidence there is for biases and residual confounding that may be affecting study results.

Biases and residual confounding are inherent in observational study designs to varying degrees. The starting premise is that these are the most logical explanations for the observed association and in order to conclude with reasonable scientific certainty that the association is causal, there must be evidence that these biases and residual confounding are minimal. In other words, if there is evidence of residual confounding and biases, the epidemiology studies would not allow one to conclude with scientific certainty that the association is causal.[30] It is worth mentioning that it is not appropriate to expect an observational study to prove there is not a causal relationship. The starting scientific premise is that there is no causal association, and it must be proved that there is one.

Since all the epidemiologic evidence at issue here is observational (versus having randomized data) with either no or weak associations, any causal assessment must generally be more demanding, requiring a greater number of Hill criteria to be met, with more convincing evidence.[30] As mentioned by many of plaintiffs' retained experts, it is not required that each criterion be met. Rather, the criteria provide a framework for integrating and interpreting data across all existing evidence arising from cell line, animal, translational and human studies. My primary expertise lies in the critical appraisal of the conclusions that can be drawn based on data contained within and across human studies. I focus on the evidence in the epidemiologic data versus the mechanistic and laboratory data. However, the relatively weak evidence for a casual association that can be obtained from the observational epidemiologic data demands stronger evidence in the cell line, animal and translational studies for how perineal talcum powder exposure leads to ovarian cancer. There needs to be convincing mechanistic data that support the components implied by the biological plausibility hypotheses that have been put forward. These data need to meet the coherence criterion described above in order to reach the conclusion of causality with scientific certainty.

In my evaluation of the epidemiology data, I primarily assess the degree to which the criteria of strength of association, consistency of the association, temporality, and biologic gradient have been met. If the strength of the association is weak or modest (say a risk ratio under 2), epidemiologists require more of the additional criteria to be met in order to reasonably rule out a spurious association that is a consequence of the inherent biases and residual confounding in the observational studies.

In the remainder of the report, I (1) review the information available at the time of the 2010 IARC report, (2) review subsequent information that has become available since the report and

whether it does or does not differ from the previous data, (3) assess the opinions rendered by some of plaintiffs' experts, and (4) offer my opinion based on my analysis of all the information I reviewed.

6 REVIEW OF THE EPIDEMIOLOGY DATA

For my review, I started with the seven meta-analyses[33-39] and the one pooled study[20] to identify the initial set of studies published that were relevant to perineal/genital talcum powder exposure and its potential association with the development of ovarian cancer. In particular, I was interested in any study that involved a form of genital/perineal talcum powder exposure, including application to the perineal, genital, or rectal area and/or use on sanitary pads, diaphragms, underwear, tampons, or condoms. There were varying definitions across the different studies with respect to genital/perineal exposures identified. One meta-analysis only pertained to talcum powder application to diaphragms.[40] Next, I undertook my own search of the literature to identify whether there were additional studies that were not contained within the meta-analyses or pooled study relevant to perineal talcum powder exposure and ovarian cancer. I did not identify any additional studies. My review was of 30[5] case-control studies[3,4,14,33,35,41-64], three cohort studies[10-13,65] (comprising five publications because one was an update to the Nurses' Health Study cohort[12] and the other analyzed a subset of women in the Nurses' Health Study[65]), one pooled analysis,[20] and seven meta-analyses.[33-39] Subsequently, I was provided a draft of another meta-analysis conducted by Taher et al.[66] that has not yet been published. In addition, I reviewed the IARC report.[2] I am confident that my review is comprehensive and contains the highest-quality studies published in the highest-impact journals. If there are any studies I did not find, they would be of lower quality and likely with relatively small sample sizes and therefore it is unlikely that any such study would alter my opinion.

6.1.1 STRENGTH OF ASSOCIATION

This criterion does not have a hard threshold. There is no cut-off value for the magnitude of an association between an exposure required for the relationship to be causal. However, it is the case that larger magnitudes of association in observational studies are more likely to reflect a causal relationship, whereas smaller associations are likely to reflect biases and confounding inherent in the observational study designs. Most epidemiologists regard relative risks (either odds ratios or risk ratios) that are less than 1.5 to be weak relationships.[1,32,67,68] Although there are instances in which ratios under 1.5 are established to be causal based only on observational data, there are more instances where they are spurious due to confounding or biases.[67] When relative risks of an association are relatively small, it is necessary to rule out residual confounding and biases, making the role of other criteria more important.

The reported association (odds ratio) between perineal/genital talcum powder exposure and ovarian cancer across the case-control studies ranges from approximately 0.92 to 1.97. (The upper value is statistically significantly greater than 1.0; there are some higher non-significant values that have been reported.) The reported association (relative risk) across cohort studies ranged from approximately 0.73 to 1.12 and none of these associations is statistically significantly different from 1. There was one pooled analysis[20] and it reported a modest statistically significant association of 1.24. The meta-analyses all report statistically significant associations between approximately 1.22 to 1.35. The exposure definitions differed across the studies from ever/never to regular use, which was also defined differently across studies.

While it is true that weak associations may arise if an exposure is a causal agent of an outcome if other Hill criteria are satisfied, the ultimate public health impact does not provide evidence of whether the exposure is causal or not. One plaintiffs' expert[15] has indicated that there have been instances in which public health recommendations were based on observations of weak associations. However, the mere fact that precautionary recommendations are made is not evidence that the associations are causal. Many of the examples cited by plaintiffs' experts have not been demonstrated with reasonable certainty to be causal, such as alcohol and risk of post-menopausal breast cancer or air pollution and cardiovascular disease. In other examples cited, the recommendations were based on data from randomized trials, which essentially are free of residual confounding and yield the strongest evidence of a causal relationship: e.g., estrogen-progestin menopausal hormone therapy (HT) and breast cancer risk, and the prevention of skin cancer through the use of sunscreen. For clinical trial data, the residual risk has been minimized by randomizing patients to treatment and control groups. Hence, there is a high likelihood that any significant association that is observed is due to the assigned treatment (or exposure); there is little concern regarding a spurious result due to bias or confounding, and so the size of the association is not an issue. Thus, the association between sunscreen and reduced skin cancer risk, for example, has been established as causal despite relatively small associations because of data from randomized trials and not because recommendations have been made on the basis of the association. Another plaintiffs' expert cites similar examples of small associations that are deemed causal and concludes that there is similar evidence for talcum powder and ovarian cancer as there is for passive smoke exposure and lung cancer.[69] It is correct to conclude that the associations are of similar magnitude, but incorrect to conclude because one is accepted as causal, so should the other based solely on the similar size of the associations. The mere fact that there have been weak associations established as causal does not furnish a sufficient basis for concluding that perineal/genital exposure to talcum powder causes ovarian cancer.

Another plaintiffs' expert states that the association between perineal talcum powder use and ovarian cancer is strong because of the public health impact overall.[69,70] Specifically, Dr. Smith-

Bindman concludes that because a very large number of ovarian cancers are purportedly caused by talcum powder, and talcum powder use provides no medical benefit, the Hill criterion of strength of association is important and met. However, these statements employ circular reasoning because they assume that the relationship between talcum powder and ovarian cancer is causal, when ascertaining causality is the entire purpose of the Bradford Hill inquiry. Only if the association were causal would there be a considerable public health impact; therefore, the possibility that there could be a considerable health impact if causation were proven is not evidence that the association between the exposure and subsequent development of disease is strong. Determining the strength of the relationship between an exposure and a disease is not made on the basis of the potential public health impact.

Smith-Bindman also misinterprets why the strength of an association is important. She states that although a larger association between exposure and disease may be easier to identify, this does not mean that it is more likely to indicate causality or importance. That is not correct. As I describe above, the issue with the strength of an association in observational studies is that smaller associations are more likely to arise from inherent confounding and biases in the study design. It is not that smaller associations are harder to detect and therefore less likely to be causal.

Another plaintiffs' expert argues that in a rare disease such as ovarian cancer, it is not uncommon to observe relatively small associations that are causal.[71] This is not true. The prevalence of the disease does not impact the strength of an association. Even for rare diseases, an association of 1.3 or less is still considered small and with a large likelihood of being spurious, without considerable supporting evidence to the contrary. The level of evidence for causality is not relaxed in instances of rare diseases, even in the case of deadly diseases such as ovarian cancer.

It is my opinion that the association between perineal/genital talcum powder exposure and ovarian cancer is about 1.3, based on the case-control studies, and that there is no statistically significant association demonstrated in the cohort studies. This means it is a relatively weak association that is likely to be spurious, arising from residual confounding or inherent biases. As such, this increases the importance of other criteria in the Hill framework for establishing that the relationship is causal.

6.1.2 Consistency of Results

Given the relatively weak association between perineal/genital talcum powder exposure and ovarian cancer as reported in some of the case-control studies, this criterion is quite important. Specifically, if there is a lack of inherent confounding and biases in the observational studies, the results across the different study designs should be consistent if the relationship is causal. There are three different designs of the primary studies: case-control using population controls,

case-control using hospital controls and prospective cohort studies. Consistency among meta-analysis data is not as informative since the meta-analyses synthesize subsets of the same studies. Obviously, more recent meta-analyses will contain more studies than earlier one because more studies have been published in the intervening time. Typically, more recent meta-analyses essentially incorporate all the studies contained in earlier meta-analyses and add studies published subsequently. Since meta-analyses encompass essentially the same set of studies (if performed about the same time) or subsets of studies contained in more recent meta-analyses, it would be expected that they yield similar results.

There is considerable variability among the estimates of the association between perineal/genital talcum powder exposure and ovarian cancer for the case-control studies. As mentioned above, the results for case-control studies range from 0.92 up to 1.97, which was statistically significant. Looking across all the results of all the case-control studies, the range is from 0.92 to 3.90, where 3.90 was not statistically significant. Clearly the results are not consistent in terms of the reported magnitude of association across the case-control studies. The largest reported association is almost 4 times greater than the smallest reported association. One issue is that the not all results were statistically significant, but this could be driven by sample size. On the other hand, the results across the cohort studies for the association between perineal/genital talcum exposure and ovarian cancer are consistent in that none of the results is statistically significant for the different cohorts: Nurses' Health Study, Women's Health Initiative, and the Sister Study. The magnitudes of the relative risks were also relatively consistent rating from 0.73 to 1.12; the largest is about 1.5 times greater than the smallest.

A possible explanation for the wide range of associations within the case-control studies is the use of different control populations. In selecting a control population, the ideal is to match the cases on all risk factors for the outcome of interest other than the exposure being investigated. For this study, it would mean selecting a control group that is similar to the case group with respect to established ovarian cancer risk factors such as age, nulliparity status, germline mutational status (e.g., BRCA1/2), and family history of ovarian cancer. Matching to such a degree is typically not possible in a case-control study. And in fact, most talcum powder case-control studies only matched for age and perhaps geographic residence of the case. An obvious difference between population controls and hospital controls is that the population controls are generally healthier than hospital controls. However, if there truly were a causal relationship, it would be expected to be seen in different control groups unless there is compelling evidence that a control group is biased toward having women with more ovarian cancer risk factors than the cases. The range of values for case-control studies with hospital controls was 1.13 to 1.70, and none of the results was statistically significant. This range is considerably smaller than what

is seen in studies with population-based controls. At the very least, this suggests that the wide range is not due to the inclusion of hospital-based controls.

The larger inconsistency is between the case-control studies and cohort studies. It is well established (as discussed above) that there is more potential for confounding in case-control studies compared to prospective cohort studies since prospective cohort studies are not prone to participant selection bias and recall bias with respect to the exposure, which is why they are considered to yield a stronger level of evidence than case-control studies. And here, not only were the magnitude of the associations meaningfully different, the association was not found to be statistically significant in the cohort studies. Specifically, according to two recent meta-analyses,[38,39] the estimates of the association of ever exposure of talcum powder to the perineal/genital region versus never use for the case-control studies was 1.26 (95% CI: 1.17 to 1.35) and 1.35 (95% CI: 1.27 to 1.43) compared to 1.02 (95% CI: 0.85 to 1.20) and 1.06 (95% CI: 0.90 to 1.25) for cohort studies. This divergence is all the more striking in light of the fact that the lack of statistical significance in the meta-analyses of the prospective cohort studies is not due to lack of power. Across the three different prospective cohort studies, there were approximately 1,400 women diagnosed with ovarian cancer and more than 200,000 women who were not diagnosed with ovarian cancer. This is in the range that Narod[72] proposes is needed to have sufficient power in a cohort study, although he does not provide a power calculation to support this number. The power to detect a hazard ratio of 1.20 or larger is over 90%, with a two-sided level of significance of 0.05. Clearly, there is sufficient power for an association of 1.26, that observed in the case-control studies, to be found statistically significant. This means that it is very likely that the true association within cohort studies (if any) is less than 1.20. In fact, the Berge et al.[38] study found that there was a statistically significantly different association for the perineal/genital talcum powder exposure and ovarian cancer between the case-control studies and cohort studies (p-value = 0.007). There is a clear inconsistency between the different study types, with case-control studies yielding a statistically significant association ranging from 1.26 and 1.35, and cohort studies yielding a non-significant association ranging from 1.02 to 1.06. Hence, there is no evidence of a causal relationship because the results are inconsistent.

Arguments have been made by all of plaintiffs' experts that the results are consistent. Some experts emphasize what they see as the relative stability of the estimates across time, in diverse populations and across diverse study designs.[70,71] Unfortunately, they do not indicate what is meant by relative stability. A range of the smallest association to the largest being four times different is not an indication of stability of the magnitude of association. Furthermore, there was a considerable difference in strength of the association yielded by case-control studies and cohort studies. Other plaintiffs' experts say the results are consistent because they consistently produced a risk ratio > 1[73,74] or > 1.1.[15] This is quite a broad metric because the

results that cover a range of 100-fold from smallest observed value to largest observed value would meet this criterion. Furthermore, plaintiffs' expert Dr. Siemiatycki argues that if there was no causal relationship, one would expect to see as many risk ratios lower than one as there are higher than one. This would only be true if there were no residual confounding or biases within studies, which is not true for observational studies. In particular, if there were clinical trial data, it then would be expected that roughly half the studies would have a risk ratio less than one and half greater than one if the relationship were not causal. However, it is likely that the case-control studies have recall biases as well as other residual confounding, which would mean that they are consistently estimating a biased association. Evidence of this is that the cohort studies yield a different result.

Other evidence cited by plaintiffs' experts of consistency is that the values of the meta-analyses are similar.[73] As discussed above, since these studies analyze overlapping sets of studies (sometimes essentially the same set of studies), it would be expected that they yield similar estimates of the strength of the associations. The consistency of the estimates across meta-analyses is uninformative for evaluating Hill's consistency of the association criterion.

Another plaintiffs' expert[15] argues that since the Penninkilampi[39] study did not detect statistically significant heterogeneity across the studies, as measured by a statistical non-significant p-value for the I^2 statistic, this is evidence of the consistency of results. This is not a true measure of the consistency of results, for several reasons. The first is that there are more than 25 case-control studies and only three cohort studies. The value of the heterogeneity statistic would be driven by the vast majority of case-control studies, which themselves encompass a four-fold range. Specifically, if the cohort studies were removed and the heterogeneity statistic were recomputed, it would not change by much because only three studies out of 28 were removed. Secondly, a non-significant statistical result for heterogeneity is not proof of lack of heterogeneity. It merely indicates that heterogeneity was not detected. In general, when a result is not statistically significant (i.e., the p-value is greater than 0.05), the only conclusion that can be made is that no difference was detected. It cannot be concluded that there is evidence of no difference because the result could reflect insufficient power to detect a difference. Finally, a test for heterogeneity is not a valid approach for determining whether the results of the case-control studies have different estimates of association than do the cohort studies. The appropriate statistical analysis to address this question is to test for an interaction between exposure and study type (case-control versus cohort). If this interaction term is statistically significant, it means that the association in case-control studies differs from the association in cohort studies, or the observed associations are inconsistent. Such an analysis was performed by Berge et al.,[38] and it was found that case-control studies yield significantly different associations than the cohort studies (p-value = 0.007); looking at the pooled estimates

of association, there was a significant association between perineal talcum powder exposure and ovarian cancer for case-control studies but not for the cohort studies.

A final argument made by plaintiffs' experts is that the level of evidence in the cohort studies is weaker than the level of evidence in the case-control studies.[15,73] The contention is that cohort studies did not probe a woman's talcum powder exposure to the extent that was done for case-control studies. Since most case-control studies and cohort studies reported the association of ever use versus never use of talcum powder in the perineal/genital region, the amount of extensive questioning of talcum powder use likely does not matter. It is relatively easy to measure if someone ever used something and does not require in-depth questioning. Another concern expressed about the cohort studies is that they do not account for the latency period between the time the exposure was initiated and the development of ovarian cancer[15,71,73,74] This is not a valid concern because the date on which the women were asked about the use of talcum powder was not the time they first started being exposed. Many of the case-control studies indicate that women had used talcum powder for a median of 20 years for both cases and controls who reported use.[4,5,14,62] It is unlikely that usage patterns in cohort studies would differ dramatically, and therefore it is likely in cohort studies that the women who used talcum powder had been using it 10-20 or more years at that point. It was also suggested that the follow-up time of the cohort studies is too short to observe ovarian cancer development.[15,71,73,74] The power of studies is driven by the number of observed cases and, as suggested, because there were a sufficient number of cases, especially in the meta-analysis of the cohort studies, the length of follow-up in the cohort studies is not a relevant issue. The cohort data are produced by three high-quality, high-profile cohort studies that have produced a wealth of information yielding hundreds of peer-reviewed publications. There is no evidence that the accepted hierarchy of level of evidence should be reversed when ascertaining whether the association between perineal/genital talcum powder and ovarian cancer is causal or is spurious due to inherent biases and residual confounding.

It is my opinion that the consistency of the association criterion has not been demonstrated. Although the case-control studies generally report risk ratios greater than one, and a little over half of the studies had statistically significant results, the range of the magnitude of the estimate is quite large. Most importantly, there is no consistency between the case-control studies and cohort studies. Meta-analyses of case-control studies yield a statistically significant result, whereas a meta-analysis of the cohort studies indicates there is no statistically significant association. As discussed above, cohort studies eliminate recall bias and participant selection (i.e., control selection) bias that are inherent in case-control studies and lead to spurious associations. Cohort studies yield a higher level of evidence. Hill observed, "I would myself put a good deal of weight upon similar results reached in quite different ways, e.g., prospectively and retrospectively."[1] There is evidence that the observed associations are not

consistent, especially between the retrospective and prospective studies, meaning this criterion does not support a conclusion that the association between perineal/genital talcum powder use and ovarian cancer is causal.

6.1.3 Dose-response relationship

The presence of a dose-response relationship provides compelling evidence of causality. Indeed, the notion that the "dose makes the poison" is a fundamental tent of toxicology. Given that the available data are from observational studies and the association is weak, additional evidence is required to rule out a spurious association, making this criterion more important.

To establish a dose-response relationship, the necessary evidence is increasing risk with increasing dose, statistical significance and consistency. Consistency in this context includes repeated demonstration of the result across different studies, including different study designs, and different measures of dose. Since the data arise from observational studies and there is no standard measure of a dose of talcum powder exposure, surrogate measures of dose are employed. Reasonable choices of dose include the duration of time a woman used talcum powder, the frequency of applications, and the lifetime number of applications that is derived from a combination of duration of use and frequency of use. Although it would not be expected or necessary that all studies or all measures within a study would have a statistically significant dose-response relationship, it would be expected that there would be consistently increasing risk with increasing usage.

The three methods used to measure the perineal/genital talcum powder application dose across the available studies are duration of use measured in years, frequency of application measured as the number of days per week or per month a woman applied the talcum powder and the cumulative lifetime applications, typically a function of duration and frequency of use. The definitions and types of dose measurements are not standardized across the studies. Given this diversity, I concluded it would be most informative to view the results of individual studies that reported a dose-response relationship. Table 1 contains the summary by type of measure for case-control studies. The majority of studies provide no evidence of a dose-relationship – i.e., increasing risk with increasing dose measure that is statistically significant. The only statistically significant results with a dose-relationship are from Wu 2009[61] and Cramer 2016[5] (but only for frequency of use and not for duration or total cumulative applications), and Schildkraut 2016.[4] The reported p-values for the Wu, Cramer and Schildkraut results include women with no perineal/genital talcum powder exposure, which means they may only be significant because of the observed association between ever use and never use of perineal/genital talcum powder, rather than a true dose-response relationship. Specifically, it has been established that there is an association between ever use of perineal talcum powder use and ovarian cancer. In order to determine whether there is a dose-response relationship

among the users of perineal talcum powder, it is important to limit the analysis to only those users of perineal talcum powder. If this is not done, it is hard to interpret the results because it could just again be a measure of ever use versus never use. Once ever use versus never use has been established as an association, to tease out the effects of the amount of use, the analysis needs to be done only in individuals who were exposed to perineal talcum powder products to determine whether there is a dose-response relationship: i.e., whether higher exposure results in a stronger association. A more appropriate test would be to determine if the trend is significant among women who had perineal/genital talcum powder exposure, as reported in Cramer 1999.[35] This is to ensure that the inherent residual confounding and bias that exist in case-control studies is not driving the dose-relationship results. If the dose-response relationship is seen in just the users of talcum powder products, it is less likely that there was substantial recall bias in the association between ever use and never use.

TABLE 1: SUMMARY OF DOSE-RESPONSE RELATIONSHIPS REPORTED IN CASE-CONTROL STUDIES

Study	**Frequency** **Risk ratio (95% CI)**	**Duration** **Risk ratio(95% CI)**	**Total number of applications** **Risk ratio(95% CI)**
Whittemore 1988	none: 1.0 (reference) 1-20/mo: 1.27 (0.82, 1.96) 20+/mo: 1.45 (0.94, 2.22) trend for 30 uses per mo: 1.30 (0.88, 1.92)	none: 1.0 (reference) 1-9 yrs: 1.6 RR (1.00, 2.57) > 10 yrs: 1.11 RR (0.74, 1.65)	
Booth 1989	none: 1.0 (reference) rarely: 0.9 (0.3, 2.4) monthly: 0.7 (0.3, 1.8) weekly: 2.0 (1.3, 3.4) daily: 1.3 (0.8, 1.9) p-value = 0.05*		
Harlow 1992	none: 1.0 (reference) < 5/mo: 1.5 (0.8, 2.7) 5-29/mo: 1.2 (0.6, 2.2) ≥ 30/mo: 1.8 (1.1, 3.0)	never: 1.0 (reference) < 10 yrs: 1.2 (0.5, 2.6) 10-29 yrs: 1.6 (1.0, 2.7) ≥ 30 yrs: 1.6 (1.0, 2.7)	
Chang 1997	none: 1.00 (reference) < 10/mo: 1.84 (1.24, 2.73) 10-25/mo: 1.13 (0.74, 1.72) > 25/mo: 0.95 (0.61, 1.49)	never: 1.0 (reference) < 30 yrs: 1.70 (1.09, 2.64) 30-40 yrs: 1.44 (0.96, 2.15) > 40 yrs: 0.87 (0.54, 1.38)	
Cook 1997			none: 1.0 (reference) ≤ 2000: 1.8 (0.9, 3.5) 2001-5000: 1.6 (0.9, 2.9) 5001-10000: 1.2 (0.6, 2.4) > 10000: 1.8 (0.9, 3.4)

Study	Frequency Risk ratio (95% CI)	Duration Risk ratio(95% CI)	Total number of applications Risk ratio(95% CI)
Wong 1999		never: 1.0 (reference) 1-9 yrs: 0.9 (0.6, 1.5) 10-19 yrs: 1.4 (0.9, 2.2) ≥ 20 years: 0.9 (0.6, 1.2)	
Cramer 1999		never: 1.0 (reference) < 20 yrs: 1.86 (1.16, 3.00) 20-30 yrs: 1.33 (0.76, 2.30) > 30 yrs: 1.44 (0.91, 2.26) p-value = 0.48**	none: 1.0 (reference) < 3000: 1.84, (1.12, 3.03) 3000-10000: 1.43 (0.84, 2.41) > 10000: 1.43 (0.92, 2.22) p-value = 0.16**
Ness 2000		never: 1.0 (reference) < 1yr: 2.0 (1.0, 4.0) 1-4 yrs: 1.6 (1.1, 2.3) 5-9 yrs: 1.2 (0.8, 1.9) > 10 yrs: 1.2 (1.0, 1.5)	
Mills 2004	none: 1.0 (reference) rarely: 1.34 (0.87, 2.08) 1-3 / week: 1.16 (0.74, 1.81) 4-7 / week: 1.74 (1.14, 2.64) p-value = 0.015*	never: 1.0 (reference) ≤ 3 yrs: 1.01 (0.58, 1.76) 4-12 yrs: 1.86 (1.16, 2.98) 13-30 yrs: 1.45 (0.90, 2.32) > 30 yrs: 1.22 (0.72, 2.08) p-value = 0.045*	never: 1.0 (reference) Q1: 1.03 (0.59, 1.80) Q2: 1.81 (1.10, 2.97) Q3: 1.74 (1.11, 2.73) Q4: 1.06 (0.62, 1.83) p-value = 0.051*
Merritt 2007		never: 1.0 (reference) 0+ to 10 yrs: 1.13 (0.90, 1.41) 10+ to 25yrs: 1.08 (0.87, 1.34) 25+ yrs: 1.29 (1.04, 1.58) p-value = 0.021*	
Wu 2009			**none: 1.00 (reference)** **≤ 5200: 1.20 (0.77, 1.88)** **> 5200 to ≤ 15600: 1.38 (0.87, 2.20)** **> 15600 to ≤ 52000: 1.34(0.89, 2.02)** **> 52000: 1.99 (1.34, 2.96)** **p-value = 0.0004***
Rosenblatt 2011		never: 1.00 (reference) 1-9.9 yrs: 1.39 (0.85, 2.28) 10-19.9 yrs: 1.46 (0.87, 2.45) 20-34.9 yrs: 1.28 (0.78,	none: 1.0 (reference) 1-1599: 1.21 (0.71, 2.06) 1600-4799: 2.08 (1.32, 3.27) 4800-9999: 0.87 (0.50, 1.53) 10000+: 0.87 (0.48, 1.57)

Study	Frequency Risk ratio (95% CI)	Duration Risk ratio(95% CI)	Total number of applications Risk ratio(95% CI)
		2.10) 35+ yrs: 0.91 (0.51, 1.62)	
Wu 2015		per 5 yrs: 1.14 (1.09, 1.20)	
Cramer 2016	**none: 1.0 (reference) 1-7/mo: 1.17 (0.96, 1.44) 8-29/mo: 1.37 (1.05, 1.78) ≥ 30/mo: 1.46 (1.20, 1.78) p-value < 0.0001***	never: 1.0 (reference) < 8 yrs: 1.31 (1.03, 1.68) 8-19 yrs: 1.31 (1.02, 1.68) 20-35 yrs: 1.35 (1.07, 1.70) > 35 yrs: 1.33 (1.03, 1.71) p-value = 0.002*	none: 1.00 ≤ 360: 1.10 (0.83, 1.47) 361 to 1800: 1.38 (1.01, 1.88) 1801 to 7200: 1.16 (0.80, 1.66) > 7200: 1.49 (1.06, 2.10) p-value = 0.02*
Schildkraut 2016	**none: 1.0 (reference) < daily: 1.12 (0.80, 1.58) daily: 1.71 (1.26, 2.33) p-value < 0.01***	**never: 1.0 (reference) < 20 yrs: 1.33 (0.95, 1.86) > 20 yrs: 1.52 (1.11, 2.07) p-value = 0.02***	**none: 1.00 < 3600: 1.16 (0.83, 1.63) > 3600: 1.67 (1.23, 2.26) p-value < 0.01***

The shaded cells indicate studies that reported a dose-response.

Abbreviations: The risk ratio may either be a relative risk (RR) or an odds ratio (OR); CI is confidence interval; mo is month; yrs is years; Q1 is the first quartile; Q2 is the second quartile; Q3 is the third quartile; Q4 is the fourth quartile

* the test for trend includes the never/none category

** the test for trend does not include the never/none category

The dose-response relationships reported in the cohort studies are summarized in Table 2. Although the Gonzales 2016 study measured frequency of use, this information was not reported in the manuscript.[13] The Gates 2010 study[12] updated the results of the Nurses' Health Study originally reported in Gertig 2000.[10] None of the cohort studies demonstrated a dose-response relationship.

TABLE 2: SUMMARY OF DOSE-RESPONSE RELATIONSHIPS REPORTED IN COHORT STUDIES

Study	Frequency Risk ratio (95% CI)	Duration Risk ratio (95% CI)
Gertig 2000[10]	none: 1.0 (reference) < 1/week: 1.14 (0.81, 1.59) 1-6/week: 0.99 (0.67, 1.46) daily: 1.12 (0.82, 1.55)	
Houghton 2014[11]		never: 1.0 (reference) less than 9 years: 1.23 (0.98, 1.54) 10 or more years: 0.98 (0.75, 1.29)
Gates 2010[12]	none: 1.0 (reference) ≥ 1/week: 1.06 (0.89, 1.28)	

Abbreviations: Risk ratio is either a relative risk (RR) or a hazard ratio (HR); CI is confidence interval

The two most recent meta-analyses and the one pooled analysis are summarized in Table 3. The Terry 2013[20] study showed a slight dose-response relationship with numerically increasing ovarian cancer incidence with increasing frequency as measured by quartiles of total applications. However, this was not found to be statistically significant with a test for trend that did not include never users, the appropriate test. The test for trend is a test to determine whether there is an increase across the different levels. As explained above, in order to determine whether there is increasing association with increasing exposure, only individuals who are exposed should be included in the analysis so that we are sure we are not re-establishing the association between ever exposure versus never exposure. Because the p-value that excluded never users was not statistically significant, there is no increasing association of more perineal talcum powder and ovarian cancer in this study. The Berge 2018[38] study found a significant relationship with the 10-year increments of talcum powder use and with one day of use increment per week of talcum powder and increased ovarian cancer incidence. What this means is that for each additional day per week of use, there was a statistically significant association of 5% increase in relative risk. However, it is not possible to examine whether the relationship is linear because the analysis also includes women who have not used talcum powder, and thus the dose-response finding might be driven by the association between ever use and never use in the case-control studies. The correct analysis would be to determine whether there is an increased association among the women who were exposed to perineal talcum powder and ovarian cancer per each additional day of use per week. Penninkilampi 2018[39] reported the result for duration separately for case-control and cohort studies and reported the total number of applications in the case-control studies. The long-term use (compared to not long-term use, which included never users) was statistically associated in the analysis of the case-control studies, but was not found to be associated in the cohort studies. Although the relative risk ratio is numerically greater for > 3600 total applications compared to < 3600 applications, there is considerable overlap of the corresponding 95% confidence intervals, meaning that these differences are likely not statistically significant.[75] This is so because when there is considerable overlap between two sets of confidence intervals, there is no evidence that the relative risks differ, and if a p-value were computed, it would be non-significant (e.g., greater than 0.05). Note that 3,600 applications roughly correspond to daily use of talcum powder for 10 years. Since there is considerable overlap between the confidence intervals, this supports the possibility that the statistical significance of the long-term use is a consequence of the association between ever use and never use.

TABLE 3: SUMMARY OF DOSE-RESPONSE RELATIONSHIPS REPORTED IN THE META-ANALYSES AND POOLED STUDY

Study	Frequency Risk ratio (95% CI)	Duration Risk ratio (95% CI)	Total number of applications Risk ratio (95% CI)
Terry 2013			none: 1.0 (reference) Q1: 1.14 (1.00, 1.31) Q2: 1.23 (1.08, 1.14) Q3: 1.22 (1.07, 1.40) Q4: 1.32 (1.16, 1.52) p-value = 0.17*
Berge 2018	**none: 1.0 (reference) per 1 time/week: 1.05 (1.04, 1.07)**	**never: 1.0 (reference) duration per 10 years: 1.16 (1.07, 1.26)**	
Penninkilampi 2018 case-control		**never: 1.0 (reference) long-term use: 1.29 (1.13, 1.47)**	none: 1.0 (reference) < 3600: 1.32 (1.15, 1.50) > 3600: 1.42 (1.25, 1.61)
Penninkilampi 2018 cohort		never: 1.0 (reference) long-term use: 0.98 (0.75, 1.29)	

The shaded cells indicate studies that reported a dose-response.

Abbreviations: Risk ratio is either a relative risk (RR) or an odds ratio (OR); CI is confidence interval; Q1 is the first quartile; Q2 is the second quartile; Q3 is the third quartile; Q4 is the fourth quartile

* the test for trend does not include the never/none category

Overall, the evidence for a dose-response relationship is not consistent across the case-control studies, with most studies not even numerically demonstrating increasing risk across increasing dose, for whichever measure is used. Examples of this include: (1) Cook 1997, where the risk for $\leq$ 2000 applications (lowest category) was 1.8 and the risk for >10,000 applications (highest category) was also 1.8; and (2) Mills 2004, where the risk for lowest quartile for total applications was 1.03 and the risk for the highest quartile for total applications was 1.06. It also is not consistent across the different measurement types. In fact, some of the case-control studies indicate that more exposure yields a smaller association with ovarian cancer (Booth,[45] Harlow[33]; based on frequency, Chang[51]; for both frequency and duration, Cook,[52] Wong,[55] Cramer 1999[35]; for duration and total number of applications, Ness,[3] Mills[57]; for all three measures, Merritt,[59] Rosenblatt,[62] and Cramer 2016[5]; and for total applications; see Table 1). There is no evidence of a dose-response relationship in the cohort studies, and some studies indicate a lower association with ovarian cancer for higher exposures (Gertig,[10] Houghton[11]; see Table 2). The meta-analyses also do not yield consistent evidence of a dose-response relationship. In the Berge 2018 study, the association observed may be driven by the

association between ever use and never use. This is also true for the long-term result in Penninkilampi 2018 for the case-control studies. There also was a lack of dose-response relationship reported for total number of applications.

Many of plaintiffs' experts claim that most or the majority of studies found a dose-response relationship,[15,70,73] but do not provide a demonstration of this. As can be observed in the tables above, a minority of the studies potentially show a dose-response relationship. It is also argued that the lack of a consistent dose-response relationship could be explained by a threshold effect.[70,73] However, if there is a threshold effect, which is very uncommon in cancer, studies should yield a consistent result for what the threshold is, along with biological evidence (cell line and animal models) that this is the type of the relationship. In particular, it seems unlikely that if a woman used perineal/genital talcum powder once, she has the same increased risk of developing ovarian cancer as a woman who used perineal/genital powder daily for 20 years, even assuming there is a causal relationship. Looking at the data, this would be the only plausible threshold value.

One of the studies that fails to find a dose-response relationship is Huncharek 2003,[36] which reported a relative risk for the association between the lowest level of exposure and ovarian cancer of 1.83, versus an association of 1.21 for the highest level of exposure. This study has been criticized by plaintiffs' expert Dr. Zambelli-Weiner.[76] While I agree that there are numerous errata in the manuscript, most of which are superficial and not uncommon in scientific papers, the analyses performed by Zambelli-Weiner also fail to establish a dose-response relationship. Specifically, although the estimates of the risk ratios reported in the manuscript cannot be replicated from the information provided by the authors, the analyses performed by plaintiffs' expert as part of her effort to illustrate the posited flaws in the Huncharek paper had different estimates of the risk ratios but still did not provide evidence of a dose-response relationship.

In summary, there is no evidence of a dose-response relationship (linear or threshold) across the available information. The results across the different measures are not consistent and only a few of these demonstrate a relationship. The few studies that suggested a dose-response were case-control studies. None of the cohort studies observed a dose-response relationship, and cohort studies provide a higher level of evidence than do case-control studies.

6.1.4 Temporality

The question of temporality is whether there is evidence that the perineal/genital talcum powder exposure occurred prior to the development of ovarian cancer. This is clearly true for the cohort studies in that when women were asked about their exposure, many had been using talcum powder products for years. Women who had developed ovarian cancer prior to being

asked about their talcum powder exposure were excluded from the analyses. For the case-control studies, it is also likely that women had been exposed to perineal/genital talcum powder starting years before their ovarian cancer was diagnosed. Although it might be true that some of the women started using talcum powder as a consequence of their ovarian cancer, e.g., to alleviate side effects of treatment, and incorrectly reported they used it prior to their cancer, this is likely a small proportion and would not have a substantial impact on the reported association. This is the one criterion that must be satisfied in order to consider whether an association is a causal relationship because no association can be considered causal if the outcome occurs before the exposure. This is a necessary condition to be met, but it alone is not sufficient for establishing causation. Overall, I find that this criterion has been satisfied.

6.1.5 OTHER CRITERIA

The other Hill criteria have somewhat less focus on human studies and are briefly reviewed here. **Specificity** implies that there is essentially a one-to-one correspondence between a particular exposure and a specific disease. If it there is evidence for this, it would increase the likelihood that an observed association between perineal/genital talcum powder exposure and ovarian cancer is causal. However, as discussed above, this has less relevance because it is known that diseases arise from a complex process, meaning that it would not be expected that all ovarian cancers would arise from a single cause. Another aspect of specificity would be that only perineal/genital talcum powder exposure would be associated with the development of ovarian cancer versus other uses of talcum powder. However, this is not the case. There have been case-control studies that observed associations of similar magnitude of non-perineal/genital talcum powder use and ovarian cancer, most of which were statistically significant.[3,4,39,61] Other lifestyle choices that have been found to be associated with ovarian cancer, with similar or greater associations than perineal/genital talcum powder use, include douching[13] and coffee consumption.[43] This illustrates the difficulty of establishing whether an observed association of a lifestyle choice and a disease is causal or spurious due to residual confounding or inherent biases in observational study design. Overall, there is no evidence provided by this criterion with respect to whether the association between perineal/genital talcum powder use and ovarian cancer is causal.

The biological mechanism that has been proposed is that particles within talcum powder can migrate up the genital tract to the fallopian tubes and ovaries.[15,70,71,73,74] Once there, it purportedly elicits an inflammatory response that initiates cancer development. Evidence for the **biological plausibility** of this would require a demonstration that only women who use perineal/genital talcum powder have embedded particles in ovary tissue, and the women who use more talcum powder have a higher risk (and perhaps greater quantity) of embedded particles. Another aspect that would need to be shown is that any inflammation associated with the development of ovarian cancer is observed in ovarian tissue that has embedded talcum

powder particles. The current state of cancer research would allow these aspects to be demonstrated if, in fact, they occurred. In addition, to establish biologic plausibility, there would need to be extremely strong effects in cell line experiments as well as animal models that isolate components of the proposed mechanism of action.

None of this evidence exists, however. While there is strong evidence that chronic inflammation can give rise to carcinogenesis in various different cancers, this is not an established mechanism for ovarian cancer. Moreover, there are no data of ongoing or chronic inflammation in perineal talc users, whether in the ovary or otherwise, or that inflammation is occurring in the presence of talc in ovarian tissue. In fact, where talc has been found in ovarian tissue, no inflammation has been found.[77] Further, studies looking at pelvic inflammatory disease (PID) and the effect of aspirin and NSAIDs have not shown a consistent effect.[59,61,78-84] What is missing is evidence that sufficient quantities of talcum particles from perineal/genital application migrate to the fallopian tubes and ovaries to cause chronic inflammation that gives rise to the development of ovarian cancer. At the present time, there are no animal models that demonstrate carcinogenesis from perineal/genital talcum powder application. Again, although there is some evidence for individual components of the proposed process (i.e., chronic inflammation gives rise to carcinogenesis in a variety of cancers), there is no demonstration for the entire process from perineal/genital talcum powder exposure to the development of ovarian cancer that has been proposed. In cancer, if large and definitive effects are not observed in cell line experiments and animal models, there likely will not be an effect in humans. For example, in cancer drug development, all drugs tested in humans have compelling cell line, animal data, and sometimes translational data, and yet, most drugs ultimately are not found to provide human benefit. All of plaintiffs' experts posit this mechanism as biologic plausibility, without providing a reference to a cogent biological mechanism or evidence by which external perineal application of talcum powder induces ovarian cancer. I understand that plaintiffs' experts rely on a study by Dr. Saed that conducted in vitro studies that involved placing talc on certain cell lines. Although the details of the study are outside my area of expertise, I understand based on his deposition that there are many gaps and irregularities in his work and that it would not provide a mechanism satisfying this criterion.[85] From my review of the pre-clinical data, there is no evidence that definitively supports the hypothesized mechanism of action for how perineal/genital application of talcum powder leads to the development of ovarian cancer. Such evidence would include talcum particles embedded in ovaries and found along the reproductive tract, with inflammation of ovaries around the embedded particles, **and** animal models that demonstrate the development of ovarian cancer when their genital region is exposed to talcum powder. This criterion is not sufficiently demonstrated.

The **experiment** criterion has not been met. As discussed above, it is not feasible to conduct a randomized trial of perineal/genital talcum powder exposure and ovarian cancer. Likewise, it also is not feasible to perform an experiment or study where a group of women who use talcum powder in the perineal/genital region cease the exposure and another group does not cease the exposure and they are followed over time. As such, there are no human experimental data available that would support a causal relationship. This criterion is uninformative with respect to whether the association between perineal/genital talcum powder exposure and ovarian cancer is causal.

There is no analogy for perineal/genital talcum powder exposure and ovarian cancer. Some plaintiffs' experts posit an **analogy** with asbestos, either through the mechanism by which asbestos causes ovarian cancer[15,71,74] or the chemical similarity between talc and asbestos.[70,73] But for this analogy to hold (and moreover, if asbestos is present in talc), one would expect an association between talc exposure and mesothelioma, which is a signature disease for asbestos. But plaintiffs' experts have not identified any studies showing that talc users are at an increased risk of developing mesothelioma. And studies of miners and millers of talc – who regularly inhale talc – have not reported any such association.[86-88]

Dr. Wolf concludes that the analogy criterion is met because of similarity with other cancer risk factors through the process where cancer is initiated by a foreign agent. These include smoking and lung cancer, asbestos and mesothelioma and ovarian cancer, sun exposure and skin cancer, and HPV and cervical cancer. The latter two are not examples of a foreign body causing inflammation: sun exposure causes DNA damage and HPV is a viral infection. In any event, the proposed analogy of a foreign body causing a cancer is too broad for the analogy to be satisfied for perineal/genital talcum powder exposure and ovarian cancer risk. This criterion has not been met for perineal/genital talcum powder exposure and ovarian cancer.

The **coherence** criterion is vague and overlaps considerably with other Hill criteria. One aspect of coherence that has not been met is that if perineal/genital talcum powder exposure were a causal risk factor for ovarian cancer, it would be expected that talcum powder usage that is more proximal to the fallopian tubes and ovaries would be associated with ovarian cancer. In addition, it would be expected that women who use talcum powder on diaphragms or have partners who used talc dusted condoms would have a stronger association with ovarian cancer. The studies that investigated these associations actually found no increased risk or a protective relationship, meaning that relative risks less than one were reported.[40] In addition, if it were true that talcum powder particles cause cancer through inflammation, it would be expected that inhalation of talcum powder would result in increased lung cancer, which has not been observed. It would also be expected that perineal talc powder exposure would be associated with vaginal, cervical and endometrial cancer. However, I am not aware of any evidence of this

or of any theory as to why talc use would only affect the ovaries and not the other sites along the reproductive tract leading from the perineal to the ovaries. Finally, given that ovarian cancer has several subtypes that are often researched as separate diseases and may well have different causes, there is no coherence to the extent plaintiffs' experts contend that perineal talc use increases the risk of multiple subtypes of ovarian cancer. Hence, this criterion has not been met in terms of providing evidence of a causal association between perineal/genital talcum powder exposure and ovarian cancer.

7 EVALUATION OF DR. SMITH-BINDMAN'S META-ANALYSIS AND EXPERT REPORT

Two of plaintiffs' experts performed their own meta-analyses: Drs. Siemiatycki and Smith-Bindman. The results of Dr. Siemiatycki's analysis yielded an association of 1.28 with a 95% confidence interval of 1.19 to 1.38. He also performed a sensitivity analysis, and the resulting risk ratios were 1.26 to 1.30. The results of Dr. Smith-Bindman's meta-analysis were an association of 1.43 (95% confidence interval of 1.15 to 1.71) between regular perineal exposure and any ovarian cancer and 1.52 (95% confidence interval of 1.15 to 1.88) between regular perineal exposure and invasive serous ovarian cancer. Dr. Siemiatycki's results align with the other existing meta-analyses, whereas Dr. Smith-Bindman's results are considerably different. Since this study was not peer-reviewed, I critically reviewed this meta-analysis for explanations for the difference, as well as for the validity of the results.

7.1 SUBGROUP ANALYSIS AND HARKING

The analysis performed by Dr. Smith-Bindman is a post-hoc subgroup analysis. There is evidence in the literature regarding how subgroup analyses are prone to spurious results.[89-92] Post-hoc subgroup analyses refer to those in which "hypotheses being tested are not specified before any examination of the data."[90] Wang et al. state that "[s]uch analyses are of particular concern because it is often unclear how many were undertaken and whether some were motivated by inspection of the data."[90] Stallones observes that "[f]or the most part, the associations discovered in a subgroup analysis are large enough to attract our attention; indeed the analysis was probably engineered to maximize that value."[89] The subgroup selected by Dr. Smith-Bindman to perform her meta-analysis were women who were *regular users* and developed *invasive serous ovarian* cancer. Dr. Smith-Bindman claims it is an advantage to have a very narrow research question, and this is often true. However, it is not valid to have such a narrow question after having reviewed the data beforehand and then proposing what study will be done, especially since the subsequent study is based on the same data that were used to generate the new question. All the previous meta-analyses included most, if not all, publications on the association between perineal talcum powder exposure and ovarian cancer,

and her analysis did not uncover any new studies to analyze. Hence, this is essentially a subgroup analysis of the previous meta-analyses, motivated by findings in the previous meta-analyses. It should be noted that in her deposition taken on February 7, 2019, Dr. Smith-Bindman states that she did a stratified analysis rather than a subgroup analysis. However, a stratified analysis is one that reports the results for all the strata, not just for one particular stratum. Specifically, if there were a stratified analysis, there should be summary risk ratios for non-regular users of perineal talcum powder and for non-serous ovarian cancer. Since she did not provide these, this cannot be considered a stratified analysis, but is rather a subgroup analysis with the subgroups being: (1) individuals who were regular users of perineal talcum powder; and (2) cases who developed serous ovarian cancer.

A related concern with performing a subgroup analysis is HARKing, Hypothesizing After the Results are Known. Kerr[93] describes HARKing as "…hypotheses presented as a priori rationales for the research to be reported; that is, hypotheses that ostensibly guided the design of that research and for which the data to be described provide an independent empirical test." There are many issues that arise due to HARKing. One relevant drawback is that the proposed hypothesis cannot fail. Specifically, when an investigator knows the results of the study in advance and proposes a hypothesis consistent with those results, there is no possibility of finding a non-significant result; the fix is in. Clearly, this is not good scientific methodology. A second relevant drawback indicated by Kerr is that "HARKing promotes narrow (i.e., context and paradigm bound) new theory." A primary research goal is to develop a general theory, and HARKing may encourage a focus on explaining the narrow effect at the cost of ignoring the broader set of potentially relevant prior findings. This is applicable here since now the focus is on invasive ovarian cancer without firmly establishing lack of association with other types of ovarian cancer.

Overall, the scientific validity of focusing on a subset question after having reviewed all the data at hand is questionable. Dr. Smith-Bindman did not posit any biological plausibility as to why invasive serous ovarian cancer would be more likely to be the result of perineal talcum powder exposure. Hence, the results of her analyses are at best hypothesis-generating and cannot be determined as definitive. Essentially, her results raise the hypothesis that the association between regular users of perineal talcum powder and invasive serous cancer may be about 1.5. However, given the concerns with subgroup analyses and HARKing, this cannot be taken as evidence that the association is higher in this group, especially in light of the fact that this is the only study to find this, and it was not peer-reviewed. It should also be noted that this does not provide any evidence regarding the causality question since it is only a subgroup meta-analysis, and thus only pertains to the strength of the association within the Hill framework. Finally, these results are in contrast to what I illustrate in Table 6 below, where there is no coherent pattern supporting a stronger association between perineal talcum powder and serous ovarian

cancer compared to any ovarian cancer. It likely arises because there was further subgrouping to women who were deemed by Dr. Smith-Bindman to be regular users of perineal talcum powder.

7.2 METHODOLOGICAL ISSUES

There is also a concern that the results of Dr. Smith-Bindman's analysis cannot be reproduced. I tried to match the numbers that were used in the meta-analysis that are reported in her expert report in Figures 2 and 3.[70] Table 3 and Table 4 show the results in her report and my attempts to match the values in the original manuscripts. As can be seen, none of the confidence interval numbers can be found in the original manuscripts. This is concerning because either the number of individuals in each group or the confidence intervals are used as part of the calculation in the meta-analysis to yield a summary risk ratio, and thus errors in abstraction directly bear on the reliability of the study's results. As stated by Dr. Smith-Bindman herself in her deposition on February 7, 2019, "I think one of the hallmarks of doing a systematic review is, in fact, to have several people abstract the data points so that you can be assured that there are – that they're done as accurately as possible, with the understanding of a single data abstraction by a single person can never be perfect."[94] Later, when Dr. Smith-Bindman was asked who calculated the confidence intervals that appeared in Figure 2 of her expert report, she responded, "To the best of my knowledge, these confidence intervals came from the primary publications."[94] After a telephone call with her colleague, Dr. Jane Hall, on the evening of February 7, 2019, however, Dr. Smith-Bindman testified in her deposition on February 8, 2019, "I was quite surprised that they weren't exactly the same. They were not meaningfully different, but there was a very slight shift in the ones that are in my report. I mean, I asked Dr. Jane [sic] why that was the case. And in fact, the numbers are calculated using the standard errors in the confidence intervals and the sample size which very slightly shifts it from the reported number. So you were correct when you said the numbers are not exactly the same, and she explained that that's why that's the case."[95]

The number of individuals in each group did not appear to be available, as indicated by the exchange between Dr. Smith-Bindman and Dr. Hall, the statistician.[2] The number of individuals in each group is needed to arrive at the weights that will be used when combining the reported risk ratios in the publications that are part of the meta-analysis. In the email on September 24 referenced above, Dr. Hall indicated that she would do her best to estimate the missing information, and Dr. Smith-Bindman confirmed that she instructed Dr. Hall that "when the raw numbers for th[e] missing proportions were not available, to do her best to estimate those."[94] It

[2] This is an email with the following information (1) From: Jane Hall drjanehall@janehall-biomed.com, (2) Date: Monday, September 24, 2018 at 11:44 PM, (3) To: "Smith-Bindman, Rebecca" <Rebecca.Smith-Bindman@ucsf.edu>, (4) Cc: "Wang, Ralph" Ralph.Wang@ucsf.edu and (5) Subject: Forest Plots - Data Decisions.

is also stated in Dr. Smith-Bindman's report that the SE (standard error) was estimated using the relationship: 95% confidence interval for the OR = effect size +/- 1.96*SE.[70] This would be an incorrect calculation because the 95% confidence interval for the natural log of the risk ratio obeys the stated relationship: 95% confidence interval for **ln(OR)** = effect size +/- 1.96 SE.[96] What this means is one must take the ln, or natural log, of the 95% confidence interval to get the SE, which is on the log scale. All calculations need to be done on the ln scale and then transformed back to the original scale at the end. It is not clear what was done to arrive at the estimates for the risk ratios provided by Dr. Smith-Bindman in her report because of the incorrect confidence intervals reported in Figures 2 and 3, which should be the values that were used in the calculation taken from the original manuscripts, and because of the incorrect statement of how to obtain SE for the OR. There is no clear documentation for how the weights were derived to arrive at the estimates of the ORs in Dr. Smith-Bindman's report other than Dr. Hall's statement in an email that she would do her best to estimate them.

TABLE 4: RESULTS REPORTED IN FIGURE 2 OF SMITH-BINDMAN EXPERT REPORT COMPARED TO THE ORIGINAL MANUSCRIPTS

Cited Study	**In report**	**In publication**	**Regular use definition**
Booth 1989	1.30 (0.75, 1.85)	1.30 (0.8, 1.9)	Daily
Chang 1997	0.95 (0.51, 1.39)	0.951 (0.61, 1.49)	> 25 after bath talc use per month
Cook 1997	1.80 (0.55, 3.05)	1.8 (0.9, 3.4)	> 10,000 lifetime applications
Cramer 2016	1.49 (0.97, 2.01)	1.49 (1.06, 2.10)	> 72000 applications ***[note that daily use was 1.46 (0.76, 1.48)]***
Gertig 2000	1.12 (0.76, 1.48)	1.12 (0.82, 1.55)	Daily
Harlow 1992	1.80 (0.85, 2.75)	1.8 (1.0, 3.0)	Total applications > 10,000 ***[applications >= 30/ month: 1.8 (1.1, 3.0)]***
Mills 2004	1.74 (0.93, 2.55)	1.74 (1.14, 2.64)	4-7 times per week
Schildkraut 2016	1.71 (1.18, 2.24)	1.71 (1.26, 2.33)	Any genital use daily
Whittemore 1988	1.45 (0.81, 2.09)	1.45 (0.94, 2.22)	20+ applications/month
Wu 2009	2.08 (1.14, 3.02)	2.08 (1.34, 3.23)	> 20 years and > 30 times/month

TABLE 5: RESULTS REPORTED IN FIGURE 3 OF SMITH-BINDMAN EXPERT REPORT COMPARED TO THE ORIGINAL MANUSCRIPTS

Cited Study	**In report**	**In publication**	**Histology**
Chang 1997	1.51 (0.7, 1.96)	1.51 (1.13, 2.02)	invasive ovarian cancer ***[Serous reported as 1.336 (0.96, 1.85)]***
Cook 1997	1.80 (0.55, 3.05)	1.7 (1.1, 2.5)	Serous ***[NOTE: same estimate as Figure 2 in report]***
Cramer 2016	1.54 (1.08, 2.00)	1.54 (1.15, 2.07)	Serous; > 24 talc years
Gertig 2000	1.49 (0.86, 2.12)	1.49 (0.98, 2.26)	Serous; ever daily use

Another concern is that it does not appear as though all studies were included in the analysis. In particular, it can be seen from Table 2 that the Rosenblatt 2011 study included risk ratio estimates based on the total number of applications. This study appears to have been initially considered for Dr. Smith-Bindman's analysis but ultimately excluded, although she did include Harlow 1992, which also only had total number of applications available. As seen in Table 4, the value used from Harlow 1992 is from "Total applications > 10,000" which had a OR of 1.8. The Rosenblatt 2011[62] study has the same category, "10,000+" (see also Table 2), and it reported an OR of 0.87. Again, this lower OR was not included in the meta-analysis performed by Dr. Smith-Bindman, and during her deposition, she was not able to explain why this was the case.[94] In fact, the only explanation provided was that exclusion of the Rosenblatt 2011 study did not impact the overall results.[94] This is false – the reported negative association in Rosenblatt 2011 would have lowered Dr. Smith-Bindman's reported odds ratios, as shown in the raw data from Dr. Hall that Dr. Smith-Bindman produced.[97]

The definition of what was considered to be regular use is also unclear. For example, Harlow 1992 and Cramer 2016 included values for the frequency of applications so that the value of "daily use," which Dr. Smith-Bindman indicated was the definition of regular use, could have been used. Instead, a decision was made to use the highest category for total number of applications instead for these studies. In the case of Cramer 2016, the risk ratio for daily use was 1.46, compared to the 1.49 for > 72000 total applications, which was used in the meta-analysis. In addition, it was stated that serous ovarian cancer was of interest when available. However, the risk ratio of 1.51 for invasive ovarian cancer was used from the Chang 1997 study, rather than the lower risk ratio of 1.336 for serous cancer in the same report. From her deposition, it is not clear why the higher value for invasive ovarian cancer was used rather than the value for serous ovarian cancer, which was the group of interest.

Other minor concerns raise questions about the experience of the Dr. Smith-Bindman and her statistical consultant in performing meta-analyses. Generally, the investigators do not appear to be aware of the correct technical terms that are used in such analyses. What is called a "Forrest Plot" is actually denoted as a forest (as in trees) plot. Also, Dr. Smith-Bindman technically performed a meta-analysis since she generated a quantitative estimate of the association between perineal talcum powder exposure and ovarian cancer. She states that she is performing a systematic review, which would not involve generating such a number. These are minor issues and do not impact the reported results, but merely raises the issue of how much experience the investigators (Dr. Smith-Bindman and the statistical consultant) have with respect to performing meta-analyses.

7.3 OTHER NOTED MISSTATEMENTS IN THE REPORT

There are several other misstatements or misunderstandings in Dr. Smith-Bindman's expert report. One is confusing the Bradford Hill criterion of strength of association with impact on public health. Dr. Smith-Bindman states:

> "It is frequently argued that the larger an apparent association, the more likely the association is to be real (causal) and important for epidemiological assessment. This would suggest that an OR of 2.0 is more likely to indicate causality and importance than an OR of 1.5. While this is often argued, I do not believe this is necessarily the case. If a risk factor increases the risk of disease by 50%, and the exposure is common, it will have a far greater impact on a number of people, in comparison to a rare exposure that has a higher associated OR. And if the association is truly one that increases risk by 50%, then this is the magnitude of the association that will be detected. It is not intuitive that if an exposure increases a risk by 50%, this difference is not discoverable compared with an exposure that increases risk by 100%."[70]

Dr. Smith-Bindman's statement misses the import of Bradford Hill with respect to strength of association. What Hill was expressing was the concern that smaller observed associations are more likely to arise from confounding rather than causal effects and that more care therefore needs to be taken to rule out confounding. Dr. Smith-Bindman seems to believe that strength of association relates to: (1) the ability to detect such an effect, and (2) the public health impact. This is erroneous. The strength of association criterion is not due to the ability to detect smaller effects. There are many associations reported in the literature, including the association between perineal talcum powder exposure and ovarian cancer, that have been "detected," meaning they were found to be statistically significant. That does not have anything to do with "strength" of the association. In addition, for an association to have a public health benefit, it must be causal. As explained previously, if the association is due to confounding, removing it would have no impact on public health.

Dr. Smith-Bindman also claims that the cohort studies provide a lower quality of evidence than do the case-control studies. According to Dr. Smith-Bindman:

> "The small number of cohort studies I found on the relationship between talcum powder products exposure and ovarian cancer did not focus on the details of this topic. While they may have included questions about talcum powder exposure, they were not sufficiently nuanced to provide meaningful information. Thus, in most of the cohort studies I found, measurements of exposure were poor, not specific, or inaccurate. Further, several had very short follow-up periods with data or information about the

> time before the cancer occurred. This negates an advantage of cohort studies, which is being able to learn about exposures before the cancer, eliminating recall bias."[70]

There is no evidence provided or cited that the questions used in the cohort studies were any more or less valid than those used in the case-control studies. In some cases, there were similar types of questions used in both of the study designs. Hence, there is a lack of basis for her statement that the measurements of exposure in the cohort studies were "poor, not specific, or inaccurate." As I mentioned above, the length of follow-up is not an issue because the power is driven by the number of ovarian cancer cases that were observed, which was adequate, and there is evidence that the perineal talcum powder exposure was initiated decades before the women were assessed for their exposure. It should be noted that all these differences between case-control studies and cohort studies exist across all scientific questions for which case-control and cohort studies are performed, not just the association between perineal talcum powder exposure and ovarian cancer. As I cite above, there is evidence in the literature that cohort studies provide less biased information than do case-control studies, and I have not found instances where the opposite is argued. It can be the case that a specific case-control study is performed better than a specific cohort study. However, the cohort studies used for evaluating the association between perineal talcum powder exposure and ovarian cancer are acknowledged to be high-quality studies, which have produced a multitude of publications. There is no basis for believing that, in this particular instance (evaluation of the association between perineal talcum powder exposure and ovarian cancer), case-control studies provide a stronger level of evidence than cohort studies.

It is also stated in her report that "**[t]he systematic reviews provide a remarkably consistent estimate of an approximately 30% increase in the risk of ovarian cancer associated with any talc powder products use**. The studies summarized in the systematic reviews reported consistent results with little variability and closely overlapping estimates for ovarian cancer risk due to talc use."[70] This is not surprising given that the systematic reviews were all based on subsets of the same set of studies. More recent systematic reviews/meta-analyses included all the studies included in earlier meta-analyses and meta-analyses performed at the same time period (e.g., Berge and Penninkilampi) and used essentially the same sets of studies. Hence, it would be expected that all the estimates are similar. This is not evidence of consistency of results in support of a causal association.

7.4 SUMMARY

Overall, the analysis provided by Dr. Smith-Bindman does not provide additional evidence in support of causality of perineal talcum powder exposure and ovarian cancer. Her analysis merely reports an association that is higher than that of other meta-analyses and suffers from the limitations of subgroup analyses and HARKing, which are known to lead to spurious

findings. There is no additional evidence provided in support of a causal association. There is also a methodological concern that the confidence intervals were calculated improperly. Furthermore, there is no protocol available that outlines the steps for how the studies were selected, what was selected as the definition of regular use of perineal talcum powder, and how the weights were calculated in the meta-analysis. Finally, there are other misstatements/misunderstandings in her report, of which I have highlighted a few above. Overall, I do not believe that the odds ratios from Dr. Smith-Bindman's analysis can be reproduced.

8 OTHER CONSIDERATIONS

There were a few other general considerations that formed my opinion. One is whether there is evidence that there is a stronger relationship with the most common histologic subtype of epithelial ovarian cancer: serous cancer. Although this is a subgroup analysis that has all the issues of a subgroup analysis, I address this theory because it appears in several of plaintiffs' experts' reports.[15,70,71,73] Next, I evaluated whether there is evidence of residual confounding within the observational studies. Finally, I looked at the evidence that has emerged since the IARC 2010 report to determine whether there is more evidence now than there was at the time of the report to support a conclusion that a causal relationship exists between perineal/genital talcum powder exposure and ovarian cancer.

8.1 SEROUS OVARIAN CANCER

The studies I used to determine whether there is a stronger relationship for serous ovarian cancer versus the association reported for all ovarian cancer are the two recent meta-analyses (Berge 2018[38] and Penninkilampi 2018[39]), the pooled study (Terry 2013[20]), two recent large case-control studies (Schildkraut 2016[4], Cramer 2016[5]), and three cohort study reports (Gertig 2000[10], Houghton 2014[11], Gates 2010[12]). The data are summarized in Table 4. There is only one study that reported a significant increase in the relative risk, the Gertig 2000 report of the Nurses' Health Study. Interestingly, an updated report of the results from the Nurses' Health Study (Gates 2010) no longer shows a difference between the relative risk for all ovarian cancer and serous cancer. The estimates of the relative risks between perineal/genital talcum powder exposure and any type of ovarian cancer and serous ovarian cancer are the same.

It should be noted that most of plaintiffs' experts[15,70,71,73] specifically call out the association between serous cancer and ovarian cancer, with some indicating it is a stronger association than that observed for all ovarian cancer or the other ovarian cancer subtypes. There are also differing conclusions between Drs. Siemiatycki[74] and Dr. Smith-Bindman[70] based upon their independent meta-analyses. Dr. Siemiatycki notes that "…from study to study, it is not always the same subtype that seems to have the highest or lowest relative risks." He further observes,

"[t]hus there is no persuasive evidence in these studies, taken as a whole that the effect of talc differs by histologic subtype of epithelial ovarian cancer."[74] This differs from the conclusion of Dr. Smith-Bindman who, as discussed above, states, "it is my opinion that women exposed to perineal talc powder products on a regular basis have about a 50% increase in their subsequent risk of developing invasive serous ovarian cancer…" Regarding other types of ovarian cancer, she states that, "[i]n my opinion, this risk is likely overall in about the same range as for serous cancer, but I would estimate slightly less at 40% increased risk."[70] My conclusion is similar to that of Dr. Siemiatycki. Based on the information in Table 6, there is no evidence that the association differs considerably between perineal/genital talcum powder exposure and any ovarian cancer or serous ovarian cancer. Only Gertig[10] showed a considerably different estimate for serous ovarian cancer (OR = 1.40, 95% CI: 1.02, 1.91) but when the results were updated after more follow-up in Gates[12], this difference no longer existed (OR = 1.06, 95% CI: 0.84, 1.35), indicating that the first difference was likely spurious.

TABLE 6: COMPARISON OF OBSERVED ASSOCIATIONS BETWEEN PERINEAL/GENITAL TALCUM POWDER EXPOSURES AND OVARIAN CANCER AMONG STUDIES

Study	Any Ovarian Cancer Risk ratio (95% CI)	Serous Ovarian Cancer Risk ratio (95% CI)
Meta-analyses		
Berge 2018	1.22 (1.13, 1.30)	
Penninkilampi 2018		
case-control	1.35 (1.27, 1.43)	1.34 (1.23, 1.47)
cohort	1.06 (0.90, 1.25)	1.19 (0.97, 1.47)
Pooled		
Terry 2013	1.24 (1.15, 1.33)	1.20 (1.09, 1.32)
Case-Control		
Schildkraut 2016	1.39 (1.10, 1.76)	1.38 (1.03, 1.85)
Cramer 2016	1.33 (1.16, 1.52)	1.42 (1.19, 1.69)
Cohort		
Gertig 2000	1.09 (0.86, 1.37)	**1.40 (1.02, 1.91)**
Houghton 2014	1.12 (0.92, 1.36)	1.13 (0.84, 1.51)
Gates 2010	1.06 (0.89, 1.28)	1.06 (0.84, 1.35)

Abbreviation: Risk ratio is either a relative risk (RR), an odds ratio (OR), or a hazard ratio (HR); CI is confidence interval

Dr. McTiernan observes that it is difficult to compare the results of the Gertig 2000[10] and Gates 2010[12] Nurses' Health Study publications. She states, "The first publication used 'never use' as the comparison and found a statistically significant effect for risk of serous ovarian cancer with any use of talcum powder products. The third publication combined 'never use' and 'less than once per week' into one referent category. If low frequency use increases risk of ovarian

cancer, which is entirely plausible, combining such women with never users will seriously underestimate the true relative risk associated with use of talcum powder products."[15] I do not see this as a particular problem. If there is a threshold effect, as has been put forward by some of plaintiffs' experts, then grouping no use with infrequent use should better detect an association because placing the infrequent users with regular users would make the association weaker if infrequent use is not above the threshold value. If there is a threshold value, grouping the participants this way would make it more likely to observe a significant association because it is assured that participants in the user group received enough exposure to cause disease and that the exposed group is not diluted by people with exposures at levels that would not cause disease. It should also be noted that Dr. Smith-Bindman only used participants who had regular use versus a control group with no use. Although this split is a bit cleaner because she did not just use individuals who used less than regularly, it is the same concept in that, if a threshold relationship is posited, then less than regular users should not be in the exposed group. Finally, the overall results of Gertig 2000 and Gates 2010 with respect to the association between perineal talcum powder use and ovarian cancer did not differ much: the risk ratio reported in Gertig 2000 was 1.09 and that reported in Gates 2010 was 1.06, both non-significant. Given the small change in this risk ratio, it is likely that the large change in the risk ratio for the association with serous cancer (1.40 in Gertig compared to 1.06 in Gates 2010) is not due to the different definition of the comparator groups.

8.2 Evidence of Residual Confounding and Bias

All studies have varying degrees of error. Common sources of error include confounding, biases and random chance. The error due to random chance is only examined if there is no systematic error, such as confounding or biases. Systematic error is of concern because it means estimates of association are not estimating the true underlying association. As a result, there may be no true association between an exposure and a disease but due to confounding, an association is observed. For example, there may be an association between having gray hair and ovarian cancer. This is not a true association. In reality, a woman with gray hair compared to a woman (of the same age) without gray hair would have the same likelihood of developing ovarian cancer. The underlying confounder is age. Biases occur when there are systematic issues within the study design, such as how cases are selected or recall bias. When a relatively weak association between an exposure and disease is observed in observational studies, a thorough evaluation must be made to rule out residual confounding and biases. If there is evidence of confounding and biases in the observational studies, then the importance of satisfying the other Hill criteria increases; in particular, there needs to be strong biological evidence that the exposure directly leads to the disease.[31,67]

There are several known factors associated with ovarian cancer. Some factors that have been established in the field include age, nulliparity status, use of oral contraceptives and family history of ovarian cancer. Older age is associated with increased risk of ovarian cancer. Women who are nulliparous have a higher risk of ovarian cancer. If a woman has used oral contraceptives for five years or longer, this reduces the risk of ovarian cancer. A family history of ovarian cancer increases the risk of ovarian cancer.[98-100] In all studies of the association between perineal talcum powder exposure and ovarian cancer that measured these established risk factors, there were differences between the cases and controls. In all instances of difference, the cases had a higher burden of ovarian cancer risk factors. The cases were older on average, even in some case-control studies that matched controls on age. The cases were more likely to be nulliparous, more likely to have a family history of ovarian cancer, and less likely to use oral contraceptives. Most studies adjusted for some of the ovarian cancer risk factors. This may reduce some of the effects of confounding, but statistical analyses cannot eliminate all the residual confounding. In addition, adjustments can only be made for factors that were measured, and most studies did not measure all the known ovarian cancer risk factors. On the basis of these differences, I conclude that there is residual confounding in the observational studies.

One study, Houghton 2014, assessed whether there are differences in ovarian cancer risk factors between women who used perineal talcum powder versus those who did not. Users were found to have a larger BMI on average, were less likely to have used oral contraceptives, and were less likely to have had a hysterectomy. They were also slightly more likely to be nulliparous than controls, but this did not significantly differ between the groups. These findings indicate that perineal talcum powder users differ from non-users in terms of risk factors associated with ovarian cancer. In other words, users were at more risk for developing ovarian cancer. This is additional evidence of confounding and it cannot be eliminated with statistical analyses.[16,23]

There is also evidence of inherent biases in the study design. The most compelling is recall bias. If there were no recall bias, the estimate of the association would be similar between case-control studies and cohort studies, both in terms of statistical significance and in terms of the magnitude of the association. As described above, the statistically significant association between perineal/genital talcum powder use and ovarian cancer seen across case-control studies is 1.25 or higher, whereas the cohort studies have values less than 1.10, which were not statistically significant. The reason that cohort studies provide a higher level of evidence is because they eliminate recall bias. Another source of bias is the way cases and controls were obtained. None of the case-control studies had a 100% participation rate. Some studies reported non-participation rates of 30% or higher.[5,14,62] No study provided a comparison of women who chose to participate and those who did not. Cases who had died prior to being

approached to participate in the study may have differed from controls in relevant ways. Specifically, cases who lived longer (enabling them to become part of the study) may have been healthier, which would influence lifestyle choices such as personal hygiene. It is known that controls who choose to participate in studies versus those who are eligible but do not choose to participate are generally healthier. Hence, the controls were likely to have fewer ovarian cancer risk factors than cases, which is what has been observed.

There is clear evidence of residual confounding and biases in the observational studies. Given the relatively weak association that has been observed between perineal/genital talcum powder use and ovarian cancer in some of the case-control studies, it is likely the association is spurious since residual confounding and biases exist. In order to conclude the relationship is causal, there would need to be definitive biological evidence that perineal/genital talcum powder exposure causes ovarian cancer.

8.3 NEW INFORMATION SINCE IARC 2010 REPORT

Several studies have been published since the IARC 2010 report,[2] raising the question whether IARC would make different findings today based on the new information that has become available since the time of the report. There have been several studies that have subsequently been published, including two additional cohort studies (Houghton 2014[11] and Gonzales 2016[13]), an update on the previous report from the Nurses' Health Study (Gates 2010[12]), a large pooled analysis (Terry 2013[20]), two large case-control studies (Schildkraut 2016[4], Cramer 2016[5]) and two meta-analyses (Berge 2018[38], Penninkilampi 2018[39]). At the time that the report was published, it was cited that there was a statistically significant association between perineal/genital talcum powder exposure and ovarian cancer, with the magnitude of the association in the range of 1.0 to 3.9 with a pooled odds ratio of 1.35. About half of the case-control studies had statistically significant associations, and for half the associations were not statistically significant.[37] It was also found that the single cohort study then available (Nurses' Health Study) did not observe a statistically significant association. In a subsequent published manuscript, a subset of the authors of the IARC report stated that the cohort study was "…arguably the strongest study because of its partly prospective ascertainment of exposure…"[37] The results regarding the dose-response relationship were reported as mixed. There was no significant dose response observed in the cohort study and positive dose-response relationship trends in two of the seven most informative case-control studies. In other case-control studies, "a non-significant, weakly positive trend was observed for either duration or frequency of use, but not for both. In the other three case-control studies, no consistent trend was observed, and the strongest associations tended to be seen among shorter-term or less frequent talc users."[2]

Since the IARC report, there have been two recent meta-analyses (Berge 2018 and Penninkilampi 2018) that included all the studies reported to date. These studies report the

magnitude of the association between perineal/genital talcum powder exposure and ovarian cancer as between 1.22 and 1.31, and these associations were statistically significant. This is in line with what was observed at the time of the IARC report, with perhaps a slight decrease in the association level since the pooled analysis at that time had an odds ratio of 1.35. Hence, the new meta-analyses do not substantially change the observed association in terms of either significance or magnitude. However, there have been two additional cohort studies (Women's Health Initiative and Sister Study) as well as updated results of the Nurses' Health Study. None of the cohort studies found a statistically significant association between perineal/genital talcum powder exposure and ovarian cancer. The two most recent cohort studies are consistent with what was observed in the Nurses' Health Study that was available at the time of the IARC report. In a meta-analysis of the cohort study results, Berge 2018 reports an association of 1.02 (95% CI: 0.85 to 1.20) and Penninkilampi 2018 reports an association of 1.06 (0.90 to 1.25). The additional information since the IARC report is the replication and consistency of the association observed within the initial cohort study: very small magnitude of association that is not statistically significant.

Recently, there has also been another meta-analysis, conducted by Taher et al., that has not been published yet.[66] These investigators report an overall odds ratio between perineal use of talcum powder and ovarian cancer of 1.28 (95% CI: 1.20 to 1.37). There was a significant association for the case-control studies (OR = 1.32; 95% CI: 1.24 to 1.4) and a non-significant association for the cohort studies (OR = 1.06; 95% CI: 0.9 to 1.25). Furthermore, they report a significant association only for the population-based case-control studies (OR = 1.34; 95% CI: 1.27 to 1.41), but not for hospital-based controls (OR = 0.96; 95% CI: 0.78 to 1.17). These results align with all the previous meta-analyses with little new information. These authors conclude, "Perineal use of talc powder is a possible cause of human ovarian cancer." Based on my years as a journal editor, I would not be surprised if they were asked to rephrase this conclusion to remove the phrase "a possible cause." Both of the most recent peer-reviewed and published meta-analyses (Penninkilampi et al. [39] and Berge et al.[38]) did not conclude that perineal talc powder use is a possible cause of human ovarian cancer based on the same information that was available to Taher et al.

There is additional information available regarding the potential dose-response relationship. The two recent, large case-control studies report a statistically significant dose-response relationship. Cramer 2016 only reports it for the frequency measure, but it is not observed for the duration or total applications. On the other hand, the Schildkraut 2016 study reports significant dose-response relationships for all three measures. There are a couple of issues with these findings. One is that the proper statistical test to establish whether the observed relationship is statistically significant has not been performed. Specifically, the test for trend includes individuals who were never exposed to talcum powder. In order to be scientifically

rigorous in determining whether there is a dose-response relationship, the test for trend should only be conducted among the individuals who had perineal/genital talcum powder exposure.[101] The larger concern is that these studies were performed after widespread publicity of court cases regarding an alleged association between talcum powder and ovarian cancer. Since these are case-control studies, it is quite likely that this resulted in additional recall bias, and Schildkraut did find much larger odds ratios for any genital talcum powder use and ovarian cancer for individuals interviewed after 2014.[4] The pooled analysis of case-control studies performed in the Terry 2013 study did not find a statistically significant dose-response relationship, and this analysis was based on results prior to increased publicity regarding lawsuits alleging that perineal talc use causes ovarian cancer. There is also additional information regarding dose-response relationship from a prospective cohort study. The result from the Nurses' Health Study that indicated a lack of a significant dose-response relationship was reproduced in the Women's Health Study. In fact, it was found that women who used perineal talcum powder for a longer duration had a numerically smaller association: 1.09 (95% CI: 0.88, 1.36) for nine or less years of use compared to 1.02 (95% CI: 0.80, 1.30) for 10 or more years of use, and there was no association for 20 years or greater use either.[11] It is likely that there is no statistical difference between these two associations. Finally, the two recent meta-analyses[38,39] did not demonstrate a consistent dose-response relationship because the doses were dichotomized and the lowest group contained never users. The unpublished Taher et al. meta-analysis performed a dose-response analysis. The results did not show a dose response when analyzed as frequency of use or for duration of use. For duration of use, it was found that if the use was between 10 and 20 years, the odds ratio was 1.42 (95% CI: 1.02 to 1.99) compared to an odds ratio of 1.19 (95% CI: 0.71 to 1.98) for 20 or more years of use. Hence, there is no compelling new information in support of a dose-response relationship. The results remain mixed and the recent case-control studies are likely further biased due to the publicity of the alleged association between talcum powder use and ovarian cancer. The cohort studies, which provide a stronger level of evidence, do not observe a dose-response relationship.

Overall, the most compelling new information provided by epidemiology studies since the IARC report is the addition of the two prospective cohort studies. These studies confirm what was observed in the cohort study that was available at the time of the IARC report: the lack of a statistically significant association between perineal/genital talcum powder use and the lack of a dose-response relationship. Likewise, the case-control studies and their meta-analyses continue to observe a significant association. However, the new studies, like the old, suffer from recall biases and selection biases. There is evidence that recall bias is compounded in the most recent Schildkraut case-control study due to the publicity regarding the alleged association between talcum powder and ovarian cancer. If there is no new compelling biological evidence that perineal application of talcum powder causes ovarian cancer, the current data remain consistent with the original IARC ruling.

9 CONCLUSION

It is my professional opinion that there is no evidence of a causal relationship between perineal/genital talcum powder exposure and ovarian cancer. This is based on my extensive and rigorous review of the epidemiology studies (and to a lesser extent, my review of scientific literature) and my experience and expertise in assessing studies for the level of evidence in the data. It is known that relatively weak associations are likely spurious due to residual confounding and biases, which I find to be the case here. There is evidence of recall bias and/or patient selection bias in the case-control studies because the cohort studies do not replicate the magnitude or statistical significance of the association. There is no consistent evidence of a dose-response relationship among the case-control studies and lack of evidence for a dose-response relationship in the cohort studies. Cohort studies provide stronger evidence than do case-control studies. There is evidence of residual confounding in the observational studies because ovarian cancer cases differ from controls on a host of ovarian cancer risk factors, in addition to the exposure to perineal/genital talcum exposure. Finally, there does not appear to be compelling and definitive evidence from cell line experiments, animal models and translational studies that support biological plausibility or a biological mechanism. On the basis of this, there is a lack of evidence to support a causal relationship.

My opinions are made to a reasonable degree of scientific certainty. I reserve the right to supplement or change my opinion as new information becomes available.

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EXHIBIT A

WEILL CORNELL MEDICAL COLLEGE *CURRICULUM VITAE* FORM

(REQUIRED FORMAT)

Signature (required):	Karla V. Ballman
Version date:	22 February 2019

A. GENERAL INFORMATION

Required Information:

Name: First, Middle, Last	Karla V. Ballman
Office address:	Healthcare Policy and Research LA-225 Weill Cornell Medical College 402 East 67th Street New York, NY 10065
Office telephone:	646-962-8023
Office fax:	646-962-0281
Home address:	430 East 63rd Street Apt. 12G New York, NY 10065
Home telephone:	507-301-3013
Cell phone:	507-301-3013
Beeper:	N/A
Work Email: Personal Email:	kab2053@med.cornell.edu kvballman@gmail.com
Citizenship:	USA
If not a U.S. Citizen, do you have:	Immigrant visa (green card)? Non-immigrant Visa? Type:

Optional Information (not required but helpful):

Birth date:	11/14/1960
Birth place:	St. Cloud, MN

Marital status:	Divorced
Race/Ethnicity:	Caucasian

B. EDUCATIONAL BACKGROUND

1. Academic Degree(s): B.A. and higher; institution name and location; dates attended; date of award. Expand the table as needed.

Degree (abbreviation)	Institution Name and Location	Dates attended	Year Awarded
B.A.	Macalester College St. Paul, MN	9/1979 to 5/1983	1983
Scientiæ Magister (S.M.)	Massachusetts Institute of Technology Cambridge, MA	9/1985 to 6/1991	1989
Ph.D.	Massachusetts Institute of Technology Cambridge, MA	9/1985 to 6/1991	1991

2. Post-doctoral training (include residency/fellowships): In chronological order beginning with post-doctoral training positions; include full titles, ranks and inclusive dates held. Expand the tables as needed.
N/A

3. Continuing Medical Education Courses/Certificates
N/A

4. Other Educational Experiences
N/A

C. LICENSURE, BOARD CERTIFICATION, MALPRACTICE

1. Licensure: Every physician appointed to the Hospital staff, except interns, and aliens in the US via non-immigrant visas, must have a New York State license or a temporary certificate in lieu of the license.
N/A

2. Board Certification
N/A

3. Malpractice Insurance
N/A

D. PROFESSIONAL POSITIONS AND EMPLOYMENT

1. Academic positions (teaching and research)

Title	Institution name and location	Dates held
Assistant Professor of Mathematics and Computer Science	Macalester College St. Paul, MN	8/1991 to 6/1999
Lecturer of Statistics	University of Auckland Auckland, New Zealand	1/1994 to 7/1996
Assistant Professor of Biostatistics	Mayo Clinic College of Medicine Rochester, MN	12/1999 to 7/2001
Associate Professor of Biostatistics	Mayo Clinic College of Medicine Rochester, MN	7/2001 to 10/2007
Adjunct Associate Professor of Biostatistics	University of Minnesota Minneapolis, MN	9/2007 to 7/2015
Adjunct Associate Professor	Biomedical Informatics and Computation Biology, University of Minnesota Rochester Rochester, MN	9/2010 to 7/2015
Professor of Biostatistics	Mayo Clinic College of Medicine	11/2014 to 7/2015
Professor of Healthcare Policy and Research Tenure awarded (11/2016)	Weill Cornell Medical College New York, NY	7/2015 to present

2. Hospital positions (e.g., attending physician)

N/A

3. Other Employment

Title	Institution name and location	Dates held
Actuarial Trainee	Minnesota Mutual Life Insurance Company St. Paul, MN	1983 to 1985
Consultant	AT&T Bell Labs Software Production Research Naperville, IL	1991 to 1994
Research Associate	Division of Biostatistics, Department of Health Sciences Research, Mayo Clinic Rochester, MN	1999 to 2002
Senior Research Associate	Division of Biostatistics, Department of Health Sciences Research, Mayo Clinic Rochester, MN	2002 to 2004
Senior Associate Consultant	Division of Biostatistics, Department of Health Sciences Research, Mayo Clinic Rochester, MN	2004 to 2007

Senior Associate Consultant	Division of Biomedical Informatics Department of Health Sciences Research, Mayo Clinic Rochester, MN	2005 to 2007
Group Statistician	American College of Surgeons Oncology Group (ACOSOG) Statistics and Data Center Rochester, MN	2006 to 2014
Chair	Division of Biostatistics, Department of Health Sciences Research, Mayo Clinic Rochester, MN	2006 to 2008
Consultant	Division of Biostatistics, Department of Health Sciences Research, Mayo Clinic Rochester, MN	2007 to 2008
Consultant	Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic Rochester, MN	2008 to 2015
Associate Editor	Journal of Clinical Oncology	2010 to 2017
Deputy Editor	Journal of Clinical Oncology	2017 to present
Consultant	Department of Surgery, Mayo Clinic Rochester, MN	2012 to 2015
Director of Biostatistics	Alliance Statistics and Data Center Rochester, MN	2013 to 2015
Division Chief of Biostatistics and Epidemiology	Healthcare Research and Policy Weill Cornell Medical College New York, NY	07/2015 to present

E. EMPLOYMENT STATUS (current or anticipated)

Name of Employer(s): Weill Cornell Medical College
Employment Status (choose one, delete the others): Full-time salaried by Weill Cornell

F. INSTITUTIONAL/HOSPITAL AFFILIATION

N/A

G. PERCENT EFFORT AND INSTITUTIONAL RESPONSIBILITIES

WCMC ANTICIPATED % EFFORT	(%)	Does the activity involve WCMC students/researchers? (Yes/No)
TEACHING	20%	yes
CLINICAL	0%	
ADMINISTRATIVE	40%	no
RESEARCH	40%	yes
TOTAL	100%	

INSTITUTIONAL RESPONSIBILITIES

1. Teaching (e.g., specific teaching functions, courses taught, dates: For guidance refer to Teaching Metrics table. Report your teaching activities in the 4 areas of teaching shown below. To provide a more detailed teaching report, use the Teaching Activities Report template or Educator Portfolio template (strongly encouraged). Refer to it here as an attachment (e.g., see attached), and attach it to the CV.

Didactic teaching: (e.g., lectures, continuing medical education courses, grand rounds, professional development programs, seminars, tutorials)	
Protocol Development (tutorial leader, Mayo Clinic College of Medicine) Health Sciences Grand Rounds	Dates 2008-2012
Mentorship: (e.g., mentor for medical student, graduate student, resident, clinical or postdoctoral research fellow or junior faculty projects; service as graduate student thesis advisor or committee member)	
8 M.S. candidates in the Clinical Research Master's degree program (Mayo Clinic College of Medicine) Served on five M.S. thesis committees for M.S. candidates in the Clinical Research Master's degree program (Mayo Clinic College of Medicine) Thesis advisor to 4 students in the Biomedical Informatics and Computational Biology M.S. degree program	Dates 2004-2015 2004-2015 2012-2015
Clinical teaching: (e.g., teaching in the clinic or hospital including bedside teaching, teaching in the operating room, preceptor in clinic)	
	Dates
Administrative teaching leadership role: (e.g., residency or fellowship director, course or seminar director or co-director)	
Probability and Mathematical Statistics (course director, Macalester College) Introductory Statistics (course director, Macalester College) Mathematical Modeling (course director, Macalester College) Calculus II (course director, Macalester College) Calculus III (course director, Macalester College) Applied Probability (course director, Macalester College) Mathematical Statistics	Dates 1991 1991, 1992 1991, 1992 1992 1992 1992-1998 1993-1999

Stochastic Methods in Management Science (course director, University of Auckland)	1994-1996
Decision Analysis (course director, University of Auckland)	1994-1996
Data Analysis with R (course director, University of Auckland)	1994-1996
Statistics Minor Curriculum Development (Macalester College)	1994-1995
Elementary Statistics (course director, Macalester College)	1995-1996
Linear Algebra (course director, Macalester College)	1996-1998
Senior Capstone (course director, Macalester College)	1996
Applied Multivariate Statistics (course director, Macalester College)	1997-1999
Differential Equations (course director, Macalester College)	1998
Experimental Design and Data analysis (course director, Macalester College)	1998
Introductory Statistical Method I (course director, Mayo Clinic College of Medicine)	1998
Special Topics in Health Sciences Research (course director, Mayo Clinic College of Medicine)	1999
Introductory Statistics Methods II (course director, Mayo Clinic College of Medicine)	2000-2003 2002, 2005
Clinical Trials (course director, Mayo Clinic College of Medicine)	2003-2004 2010, 2011
Introduction to Biostatistics (course director, Executive MBA/MS program, Weill Cornell Medicine)	2017-present
Biostatistics I (course director, Biostatistics and Data Science MS program, Weill Cornell Medicine)	2018-present

2. Clinical care (duties, dates: To document clinical activities use the table below or, to document extensive clinical activities use the Clinical Portfolio template (strongly encouraged). Refer to it here as an attachment and attach it to the CV.
   N/A

3. Research (duties, dates): Summarize research activities in the table below. Provide key contributions, and annotate key grants and publications or use a Statement of Key Contributions. Refer to it here and attach it to the CV.

Research Activity / Key Contributions	Dates
See Statement of Key Contributions	

4. Administrative Activities (duties, dates): Describe administrative activities in the table below. To document administrative activities more extensively use a supplemental statement, refer to it here and attach it to the CV.

Administrative Activity	Date
Education Committee Member (Health Sciences Research, Mayo Clinic)	2000 to 2002
Education Committee Chair (Health Sciences Research, Mayo Clinic)	2002 to 2007
Education Committee Member (Clinical Research Training Program, Mayo Clinic)	2001 to 2006
Executive Committee Member (Clinical Research Training Program, Mayo Clinic)	2001 to 2005
Master's Examination Committee Member (Clinical Research Training Program, Mayo Clinic)	2002 to 2015
Curriculum Committee Chair (Clinical Research Training Program, Mayo Clinic)	2002 to 2006
Data Safety and Monitoring Board Member (Mayo Clinic Cancer Center)	2003 to 2006
Clinical Studies Oversight Committee Member (Mayo Clinic Cancer Center)	2003 to 2006
Neuro-Oncology Executive Committee Member (Mayo Clinic Cancer Center)	2003 to 2010
Neuro-Oncology Protocol Planning Committee Member (Mayo Clinic Cancer Center)	2003 to 2007
Education Committee Member (Mayo Graduate School)	2004 to 2006
Executive Committee Member (Department of Health Sciences Research, Mayo Clinic)	2004 to 2008
Education Programs Curriculum Committee Member (Center for Translational Activities, Mayo Clinic)	2006 to 2008
Division Chair (Division of Biostatistics, Health Sciences Research, Mayo Clinic)	2006 to 2008
Peer Review Research Committee Member (Department of Surgery, Mayo Clinic)	2011 to 2015

Research Executive Committee Member (Department of Surgery, Mayo Clinic)	2011 to 2015
Research Committee Member (Department of Surgery, Mayo Clinic)	2011 to 2015
Data Safety and Monitoring Board Member (Department of Surgery, Mayo Clinic)	2012 to 2015
Division Chief for Healthcare Policy & Research	2015 to present
Healthcare Policy & Research Promotions Committee Member	2015 to present
Weill Cornell Medicine Data Safety and Monitoring Board (alternative) Co-Chair	2017 to present
Weill Cornell Committee of Review	2018 to present

H. RESEARCH SUPPORT

Summarize **Past Research** Support:

1. The Mayo Clinic Research Training Program funded by National Center for Research Resources (K30 RR 22296) from 06/1999 to 09/206 ; role: Associate Director
2. Risk Factors for Venous Thromboembolism in the Community funded by NHLBI (R01 HL 66216) from 04/2001 to 04/2005; role: Co-investigator
3. Angiotensin-II Blockade in Mitral Regurgitation funded by NHLBI (R01 HL 64928) fron 04/2001 to 03/2005; role: Co-investigator
4. Core 1: Statistical and Administrative Core in: Gene Therapy for Vaso-occlusive disease funded by NHLBI (P01 HL 66958) from 09/2001 to 08/2008; role: Co-investigator 5. Core B: Study Design and Analysis Core in: Molecular Markers of Glioma Initiation & Progression funded by NCI (P01 CA 85799) from 06/2001 to 05/2006; role: Principal Investigator
6. GSK-3 and Associated Pathways in PNET funded by NINDS (R01 NS 40794) from 07/2002 to 11/2005; role: Collaborator
7. Mitochondria and surgical myopreservation in aging funded by NIA (R01 AG 21201) from 09/2002 to 08/2008; role: Consultant
8. Heart Failure in the Community funded by NHLBI ((R01 HL 72435) from 01/2003 to 06/2007; role: Co-investigator
9. Flavopiridol as a Potential Therapy in Multiple Myeloma funded by NCI (R01 CA 98118) funded from 07/2003 to 06/2008; role: Co-investigator
10. MAGE-A3/HPV 16 Peptide Vaccines for Head and Neck Cancer funded by the NIDCR (R01 DE 15324) from 04/2004 to 12/2004; role: Co-investigator
11. Xenograft Model for Studying Amplified EGFR in GBM funded by NCI (R01 NS 49720) from 08/2004 to 05/2006; role: Co-investigator
12. Brain Tumor SPORE – Core B – Biostatistics funded by NCI (P50CA 108961) from 09/2004 to 08/2014; role: Core Director
13. Global Differential Expression Profiling During Sudden Tumor Progression Using the Tumor Dedifferentiation Phenomenon as a Model funded by Mayo Clinic Foundation (CR20) from 04/2006 to 06/2010; role: Co-investigator
14. Measles Virotherapy for Glioblastoma Multiforme funded by NCI (R21 CA 123839) from 08/2006 to 07/2010; role: Co-investigator
15. Utility of Serum and Tissue Biomarkers for Predicting Response to Androgen Deprivation Therapy in the Population of Men with Rising PSA Following Definitive Treatment in: SPORE in Prostate Cancer funded by NCI (P50 CA 91956) from 09/2006 to 08/2013 ; role: Co-investigator
16. SPORE in Prostate Cancer—Biostatistics Core funded by NCI (P50 CA 91956) from 09/2006 to 08/2013; role: Core Director
17. Statistical Responsibilities for American College Of Surgical Oncology Group (ACOSOG) funded by NCI (U10 CA 76001) with subcontract to Mayo from 03/2006 to 11/2014; role: Principal Investigator
18. Epigenetic regulation of temozolomide responsiveness in glioblastoma funded by NCI (R01 CA 127716) from 01/2008 to 12/2012; role: Co-Investigator
19. Correlative Science and Imaging Analysis for Z1031 funded by Breast Cancer Research Foundation (WU-09-200) with subcontract to Mayo fro m10/2008 to 09/2009; role: Principal Investigator
20. A phase III randomized Double Blind study of Adjuvant ST1571 (Gleevee) versus Placebo in patients following the Resection of primary gastrointestinal Stromal Tumor (GIST) funded by Novartis from 12/2008 to 06/2009; role: Principal Investigator
21. Mayo Comprehensive Cancer Center Grant funded by NCI (P30CA 15083) from 03/2009 to 07/2015; role: Statistician

22. Novel Biomarkers for Aromatase Inhibitor Therapy funded by NCI (R01 CA 95614) from 04/2009 to 12/2011; role: Principal Investigator
23. Optimizing Measles Virotherapy in the Treatment of Gliomas funded by NCI (R01CA 140620) from 07/2009 to 03/2011; role: Co-investigator
24. ACOSOG Community Clinical Oncology Program (CCOP) Research Base funded by NCI (U10CA 149950) from 06/2010 to 07/2014; role: Co-investigator
25. Treatment patterns of patients with newly diagnosed malignant primary brain tumors funded by Monteris Medical from 09/2010 to 08/2011; role: Principal Investigator
26. Statistical Responsibilities for American College Of Surgical Oncology Group (ACOSOG) in: Industry Supplement of Statistical Responsibilities for American College Of Surgical Oncology Group (ACOSOG) funded by Duke Clinical Research Institute from 12/2010 to 11/2011; role: Principal Investigator
27. N1037 P95HER2 expression in metastatic breast cancer patients treated with trastuzumab on N0337 and NCCTG 98-32-52 funded by BioTheranostics/BioMerieux from 10/2011 to 3/2012; role: Co-investigator
28. Part 1 N9831F-NCCTG-ICSC Validation study of Quantitative Single Gene Assessment of HER2 mRNA by qRT-PCR and Development and Testing of New HER2 Multi-Gene Signature funded by Genomic Health, Inc. from 04/2012 to 05/2015; role: co-Principal Investigator
29. Therapeutic Strategy to Slow Progression of Calcific Aortic Valve Stenosis funded by National Center for Advancing Translational Sciences (UH2TR 000954) fro 06/2013 to 07/2015; role: Co-investigator
30. Patient Centered: Risk Stratified Surveillance After Curative Research of Colorectal Cancer funded by a subcontract from a PCORI grant (CE-1304-6855) from 03/2014 to 07/2015; role: Principal Investigator
31. Post-Treatment Surveillance in Breast Cancer: Bringing CER to the Alliance funded by a subcontract from a PCORI grant (CE-1304-6543) from 03/2014 to 07/2015; role: Principal Investigator
32. Statistics and Data Center for the Alliance for Clinical Trials in Oncology funded by NCI (U10CA 180882) from 04/2014 to 07/2015; role: Co-investigator
33. Alliance NCORP Research Base funded by NCI (UG1CA 189823) from 08/2014 to 07/2015; role: Co-investigator
34. Improving How We Predict Toxicity for Older Women with Breast Cancer funded by Susan G. Komen Breast Cancer Foundation from 10/2014 to 09/2017; role: Principal Investigator (subsite)
35. Sarcoma Foundation from 11/2015 to 05/2017; role: Principal Investigator
36. Clinical and Translational Science Center (2UL1 TR000457) funded by NIH from 06/01/12 to 05/31/17; role: Co-Investigator
37. SPECs Grant in Lung Cancer (U01CA 157715) funded by NCI from 07/2012 to 06/2018; role: PI of a subcontract
38. Sarcoma SPORE—Biostatistics Core funded by NCI (5U54CA 168512) from 09/2016 to 08/2018; role: Core Director
39. Prostate Cancer Foundation study funded from 07/2017 to 08/2018; role: co-investigator

For **Current extramural and intramural research funding**, provide the following for each award:

1. Source, amount, and duration of support (dates)
2. Name of Principal Investigator
3. Individual's role in project, including percentage (%) effort

Current Research Support (duplicate table as needed):

Source	NCI (CA180882) subcontract Alliance
Amount	$172029
Duration	04/2018 to 02/2023
Principal Investigator	Mandrekar
Your Role in Project	Co-investigator (PI of the subcontract to WCMC)
% Effort	40%

Source	SU2C
Amount	$13,515

Duration	08/2017 – 06/2020
Principal Investigator	Cantley
Your Role in Project	Co- Investigator
% Effort	5%

Source	National Institutes of Health 1UL1TR002384-01
Amount	$5,319,707
Duration	09/2017 to 06/2022
Principal Investigator	Imperato-Mcginley
Your Role in Project	Co-Investigator
% Effort	6%

Source	Department of Defense (Subcontract with Duke University, W81XWH-17-1-0372)
Amount	$170,266
Duration	11/2017 to 10/2020
Principal Investigator	Harpole
Your Role in Project	Principal Investigator (Subsite)
% Effort	10%

Source	National Institutes of Health (P50 CA211024-01A1)
Amount	$134,759
Duration	07/2017 to 06/2022
Principal Investigator	Rubin
Your Role in Project	Computational Biology and Biostatistics Core Director
% Effort	3%

Source	Bill and Melinda Gates Foundation
Amount	$89,116
Duration	11/2016 to 05/2020
Principal Investigator	Lee
Your Role in Project	Investigator
% Effort	2%

Source	NIMH, ALACRITY for late- and Mid-Life Mood Disorders (P50 MH113838)
Amount	$1,014,850
Duration	09/2016 to 08/2021
Principal Investigator	Alexopoulos
Your Role in Project	Investigator
% Effort	5%

Source	NIH, Biomarkers of taxane chemotherapy response/resistance in prostate cancer (R21 CA216800-01A1)
Amount	$130,500
Duration	04/2018 to 03/2020
Principal Investigator	Giannakakou

Your Role in Project	Investigator
% Effort	2%

Source	Department of Defense, Molecular and clinical correlates with prostate-specific membrane antigen (PSMA)-targeted radionuclide therapy (W81XWH-17-PCRP-IA)
Amount	$72,380
Duration	07/2018 to 06/2021
Principal Investigator	Tagawa/Beltran/Bander
Your Role in Project	Investigator
% Effort	2%

Source	NIH/NCI, Mechanism-based Targeting of Mantle Cell Lymphoma (P01 CA2144274-01A1)
Amount	$1,166,145
Duration	09/2018 to 08/2023
Principal Investigator	Chen-Kiang
Your Role in Project	Core Leader
% Effort	8%

Source	NIH, The human distal airway aging project (U01HL145561)
Amount	$5,688
Duration	01/19
Principal Investigator	Shaykhiev
Your Role in Project	Biostatistician
% Effort	3%

I. EXTRAMURAL PROFESSIONAL RESPONSIBILITIES

i.e. – Journal Reviewer, Editorial Boards, Study Sections, Invited Presentations

Activity / Responsibility	Dates
Reviewer The American Math Monthly	1991 to 1999
Gender and Ethnic Division Committee Member North Central Cancer Treatment Group	2002 to 2005
Neuro-Oncology Committee Member North Central Cancer Treatment Group	2002-2006
Reviewer The American Statistician	1994 to 1999
Editorial board member Journal of Statistics Education	1998 to 2003
Reviewer Mayo Clinic Proceedings	2001 to 2004
Reviewer Circulation	2003 to 2006
NCI Review Panel Member Consortium Therapeutic Studies of Primary Central Nervous System Malignancies in Adults	2003, 2008
Reviewer Bioinformatics	2004 to present

NCI Study Section ad hoc Member Scientific Review Group Subcommittee H-Clinical	2004, 2007, 2008
Reviewer Cancer Research	2004 to present
Editorial Board Neuro-Oncology	20045-2014
Reviewer American Journal of Gastroenterology	2005 to 2006
Review Panel Member Academic Public-Private Partnership Program (AP4)	2005
NCI-Avon Foundation Review Panel Member PFP Awards Program	2005 to 2006
NCI Review Panel Member Advanced Proteomic Platforms and Computation Sciences for the NCI Clinical Proteomic Technologies Initiative Review Panel	2006
Executive Committee Member American College of Surgeons Oncology Group	2006 to 2012
NCI Committee Member Breast Cancer Intergroup Committee	2007 to 2009
NCI Committee Member Breast Cancer Intergroup Correlative Sciences Committee	2008 to 2009
NCI Study Section Member Scientific Review Group Subcommittee H-Clinical	2009 to 2012
NCI Steering Committee Member Gastrointestinal Stromal Tumor Working Group	2009-2013
NCI Steering Committee Member Brain Malignancies	2009 to present
NCI Review Panel Member Novel Methodologies	2006
Data Monitoring Committee Member American College of Surgeons Oncology Group	2006 to 2011
Breast Cancer Committee Lead Statistician American College of Surgeons Oncology Group	2006 to 2011
Reviewer Biometrics	2006
NIAID Review Panel Member Cooperative Study Group for Autoimmune Disease Prevention	2006
Clinical Scientific Review Committee Member American College of Surgeons Oncology Group	2006 to 2011
Reviewer International Journal of Cancer	2006 to present
NICHHD Review Panel Member Obstetrical Pharmacology Research Network-Data Coordination and Analyses Center (OPRU-DCAC)	2007
Canada Cancer Society Review Panel Grant Application Review	2007
Editorial Board Journal of Clinical Oncology	2007 to 2010
NIAID Review Panel Member Proteomics Centers for Infectious Diseases and Biodefense	2008
NIDDK Review Panel Member Hepatitis B Clinical Research Network (U01)	2008
NIH Review Panel Member Data Management and Coordinating Center DMCC for the Rare Diseases Clinical Research Network (RDCRN)	2008
NIDDK Review Panel Member Multi-disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network (U01)	2008
Data Monitoring Committee Member	2008-2012

Astra-Zeneca Phase III Trial	
Reviewer EURASIP Journal on Bioinformatics and Systems Biology	2008 to present
NCI Committee Member Clinical Trials Advisory Committee, Operational Efficiencies Working Group	2008 to 2009
NICHHD Review Panel Member Best Pharmaceuticals for Children Act Data Coordinating Center	2009
MN Partnership for Biotechnology and Medical Genomics Review Panel Member Scientific review of grant proposals	2009
NIDA Review Panel Member Data and Statistics Center for NIDA Clinical Trials Network	2009
Thoracic Cancer Committee Lead Statistician American College of Surgeons Oncology Group	2009 to 2011
Reviewer British Journal of Cancer	2009 to present
Reviewer Clinical Trials	2009 to present
Reviewer Plos1	2009 to present
NCI Review Panel Member Clinical Proteomic Technologies for Cancer Initiative: Proteome Characterization Centers	2010
NICHHD Review Panel Member Pediatric Trials Network	2010
Review Panel Member National Cancer Institute of Canada	2010
DOD CDMRP Review Panel Member	2010-2019
Data Monitoring Committee Chair University of Minnesota Iron Study	2010 to 2014
Data Monitoring Committee Member Eli Lilly 14T-MC-JVBB Trial	2010 to 2014
Data Monitoring Committee Incyte RESPONSE Trial	2010 to 2014
Associate Editor Journal of Clinical Oncology	2010 to 2017
Deputy Editor Journal of Clinical Oncology	2017-present
Reviewer Nature	2010, 2013, 2017, 2018
NICHHD Review Panel Member Systematic Review of Neonatal Medicine	2011
NICHHD Review Panel Member Maintenance of Child Health and Development Studies Name and Address Files	2011
Dutch Cancer Society Review Panel Member Scientific Grant Review	2011, 2014, 2015
Reviewer Annals of Surgery	2011 to present
Operations Committee Member Alliance Adult Cancer Cooperative Group	2011 to 2015
Scientific Concept Peer Review Committee Member Alliance Adult Cancer Cooperative Group	2011 to 2014
Data Safety Monitoring Board Chair Kanas University PAD in AA Trial	2011 to 2018
NICHHD Review Panel Member Folic Acid Supplementation and Semen Quality Trial (FAAST)	2012
NIAID Review Panel Member Pre-Clinical Pharmacology and Toxicology Studies	2012
NCI Review Panel Pre-clinical Efficacy and Intermediate Endpoint	2012

NIDA Review Panel Data, Statistics, and Clinical Trial Support for NIDA	2012, 2014
Cancer in the Elderly Committee Lead Statistician Alliance Adult Cancer Cooperative Group	2012 to 2015
NICHHD Review Panel Member Multiple Study Data Coordinating Center for DESPR	2013
Mayo Clinic Review Panel Member Microbiome Program Clinic Trial Funding	2013
NICHHD Review Panel Member Further Investigation into the Causes of Stillbirth Concept Clearance	2013
Publications Committee Member Alliance Adult Cancer Cooperative Group	2013 to 2016
Neuro-Oncology Committee Lead Statistician Alliance Adult Cancer Cooperative Group	2013 to present
FDA Medical Devices Advisory Committee Member General and Plastic Surgery Devices	2013 to present
Damon Runyon Foundation Review Panel Member Clinical Investigator Award	2013 to present
NCI Brain Malignancies Steering Committee member	2013 to present
NCI Review Panel Member PLCO Secondary Studies Proposals	2014, 2015
NIAID Review Panel Member Inner City Asthma Consortium (ICAC3)	2014
Associate Editor Neuro-Oncology	2014 to 2018
Data Safety and Monitoring Board Committee Member NIDDK	2014 to present
NICHHD Review Panel Member P01 Pre-Natal Microbiome Grant Review	2015
NIAID Review Panel Member Centers for Medical Countermeasures against Radiation Consortium (U19	2015
Cancer Research UK Review Panel Member Biomarker Project Award	2015
Statistical Associate Editor American Journal of Respiratory and Critical Care Medicine	2015 to present
Independent Data Monitoring Committee Member Ariad Phase II trial of AP26113 in non-small cell lung cancer	2015-2018
NIAMS Technical Evaluation Panel Member Clinical Studies Management and Support	2016
NIAID Scientific Review Panel Member Asthma and Allergic Diseases Cooperative Research Centers	2016
NICHD Technical Evaluation Panel Member Best Pharmaceutical for Children Act Data Coordinating Center	2016
NINDS Scientific Review Panel Member Parkinson's Disease Biomarkers Program	2016
Cancer Research United Kingdom Review Panel Member Program Project Submission	2016
Data Safety and Monitoring Board Member The Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) Trial	2016 to present
United States Army Medical Research and Material Command (MRMC) Peer Review Panel Member	2016-2018
KNOD Study Section Committee Member	2018 to present
Cancer Moonshot Initiative: Human Tumor Atlas Research Centers (U2C) review panel member	2018
Clinical Research Training Institute Summer Workshop Faculty Member American Society of Hematology	2016 to present
Cancer LinQ Publications Committee Member	2016 to present
STATS.org Statistical Advisory Board Member	2016 to present

NIH/NIAID Asthma and Allergic Diseases Cooperative Research Centers	2017
NCI Program Project Grant (P01) Review Committee Member	2017
Data Safety and Monitoring Board Member Clofazimine in the treatment of pulmonary Mycobacterium avium complex (MAC) disease trial	2017 to present
NCI Oncology E Review Panel Member	2017
ASCO CancerLinQ Research and Publications Committee Member	2017 to present
Conquer Cancer Foundation Grant Selection Committee Member	2017 to present
Independent Data Monitoring Committee Member Takeda Phase III trial of brigatinib in non-small cell lung cancer	2018 to present
NCI Moonshot Initiative, the NCI Human Tumor Atlas Network (HTAN) Review Committee Member	2018
NCI Breast Cancer Steering Committee Member	2018 to present
NCI Program Project Grant (P01) Review V Committee Member	2019

J. PROFESSIONAL MEMBERSHIPS

Include medical and scientific societies

Member/Officer/Fellow/Role	Organization	Dates
Member	Operations Research Society of America	1990 to 1993
Officer	Operations Research Society of America	1992
Member	Mathematical Association of America	1991 to 1997
Officer	American Statistical Association	2000 to 2003; 2011 to 2013
Member	American Statistical Association	2000 to present
Member	American Society of Clinical Oncology	2005 to present
Member	Society of Neuro-Oncology	2007-present
Member	International Biometric Society, East North American Region	2006 to present
Officer	International Biometric Society, East North American Region	2008 to 2011
Member	Society of Clinical Trials	2008 to present

K. HONORS AND AWARDS

Name of award	Date awarded
Pi Mu Epsilon (Math honorary) - Macalester College	1980
Phi Beta Kappa - Macalester College	1982
Magna Cum Laude - Macalester College	1983
Academic All-American, Division III Volleyball - Macalester College	1983
Fredrick Hennie II Teaching Award - Massachusetts Institute of Technology	1987
Health Sciences Research Distinguished Teaching Award - Mayo Clinic	2004
Macalester College Distinguished Alumni in Science	2015

L. BIBLIOGRAPHY

1. Articles in professional peer-reviewed journals

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5. Brilakis ES, McConnell JP, **Ballman KV**, Klee GG, Berger PB. Lack of association between plasma homocysteine and angiographic coronary artery disease in the era of fortification of cereal grain flour with folic acid. Atherosclerosis. 2002 Dec; 165(2):375-81. PMID:12417290.

6. Squires RW, Leung TC, Cyr NS, Allison TG, Johnson BD, **Ballman KV**, Wagner JA, Olson LJ, Frantz RP, Edwards BS, Kushwaha SS, Dearani JA, Daly RC, McGregor CG, Rodeheffer RJ. Partial normalization of the heart rate response to exercise after cardiac transplantation: frequency and relationship to exercise capacity. Mayo Clin Proc. 2002 Dec; 77(12):1295-300. PMID:12479515. DOI:10.4065/77.12.1295.

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10. Takemoto Y, Tanabe K, Chandrasekaran KW, **Ballman KV**, Seward JB, Belohlavek M. Single-plane and biplane echocardiography: Use of targeted scan planes improves the estimates of left ventricular volume and shape for analysis of postinfarction remodeling. J Am Soc Echocardiogr. 2003 May; 16(5):448-56. PMID:12724654.

11. Barretto S, **Ballman KV**, Rooke TW, Kullo IJ. Early-onset peripheral arterial occlusive disease: clinical features and determinants of disease severity and location. Vasc Med. 2003 May; 8(2):95-100. PMID:14518611.

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14. Brilakis ES, Berger PB, **Ballman KV**, Rozen R. Methylenetetrahydrofolate reductase (MTHFR) 677C>T and methionine synthase reductase (MTRR) 66A>G polymorphisms: association with serum homocysteine and angiographic coronary artery disease in the era of flour products fortified with folic acid. Atherosclerosis. 2003 Jun; 168(2):315-22. PMID:12801615.

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2. Editorials and Letters

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3. Chapters

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2. **Ballman KV**. Real Data in Classroom Examples. In: Teaching Resources for Undergraduate Statistics. 2000. (Book chapter)
3. **Ballman KV**. Handbook of Clinical Cancer Research. Springer 2018. (Book chapter)
4. **Ballman KV**. Predictive Biomarkers in Oncology. Springer 2019. (Book chapter)

EXHIBIT B

List of Testimony Given in the Last Four Years by Karla V. Ballman, Ph.D.

Depositions

July 21, 2017

BTG International Ltd. v. Actavis Laboratories Fl., Inc., No. 2:16-cv-05909-KM-JBC, U.S. District Court for the District of New Jersey

AND

BTG International Ltd. v. Amerigen Pharmaceuticals, Inc., No. 2:16-cv-02449-KM-JBC, U.S. District Court for the District of New Jersey

Oct. 30, 2018

In re: Viagra (Sildenafil Citrate) and Cialis (Tadalafil) Products Liability Litigation, No. 3:16-md-02691, MDL No. 2691, U.S. District Court for the Northern District of California (San Francisco Division)

Trial Testimony

July 26, 2017

BTG International Ltd. v. Actavis Laboratories Fl., Inc., No. 2:16-cv-05909-KM-JBC, U.S. District Court for the District of New Jersey

AND

BTG International Ltd. v. Amerigen Pharmaceuticals, Inc., No. 2:16-cv-02449-KM-JBC, U.S. District Court for the District of New Jersey